Neural correlates of episodic memory in healthy aging and Alzheimer's disease

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About the cover:
Synthesis nr. 9, Olga Meulenbroek
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Every synthesis is an arrangement of different elements that have several meanings. These can be figural or literal, abstract or concrete.
The image is created to look like an exhibit in a museum of natural history: a delicate butterfly, tagged and carefully placed in a frame. Besides representing Olga`s aspirations to be a taxidermist in her spare time, it stands for the research presented in this book. Central to the image is the butterfly, a Parnassia apollo or the Apollo-butterfly. The butterfly is a symbol of brittleness and Apollo is the ancient Greek god of knowledge, leading to the combination symbolizing the frailty of knowledge.
Memory is fragile and we tend to lose parts of it as we age. That is why we treasure our memories and like to fixate them, for instance in photographs, framing them and putting them up on the wall. In the cover image, the frame is important. It stands for the arduous nature of this research. Closer inspection of the frame shows a schematic skull, arachnoid mater and brain. The skull is, of course, a hefty barrier in brain research, but next to nothing in the light of the complexity of the brain. This is where the spectator can become a part of the image: the inside of the frame, with its brain like curves, is actually a maze. There is one route through this maze that connects all four corners of the frame. Enjoy exploring the brain!

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No wise man ever wished to be younger

Jonathan Swift

Irish essayist, novelist, & satirist (1667 - 1745)

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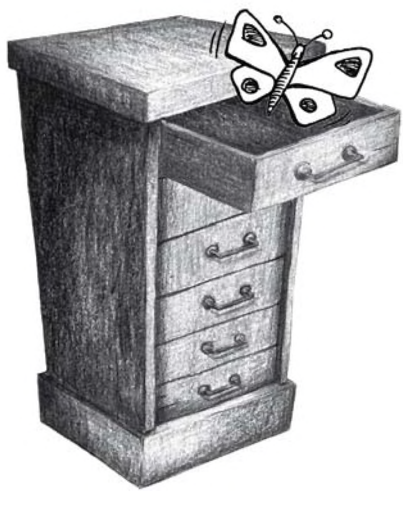
Chapter

General introduction and outline

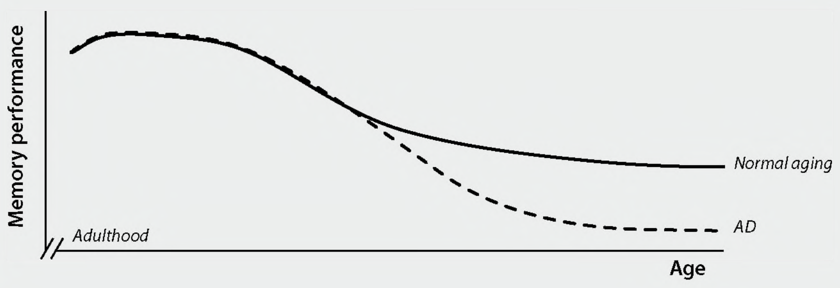


Memory is an organism's ability to store, retain and retrieve information. Without it, we would not be able to adapt our behaviour on the basis of experience. Few cognitive processes can operate effectively without a contribution from memory, which makes memory one of the key features for survival.

With age, we notice our memory declines: for example, forgetting where we parked our car or left our keys, forgetting directions to destinations, forgetting items when shopping or having difficulty remembering names. All these abilities are part of "episodic memory", which refers to the remembrance of unique events (episodes) that have associated contextual details, allowing for subjective re-experiencing (Tulving 2002). This is also described as "mental time travel", because episodic memory in some sense brings the past into the present.

The mild decline of episodic memory with aging is considered to be natural. However, severe episodic memory impairments can also occur with age, such as in the case of dementia, which is in most cases caused by Alzheimer's disease (AD). Below is a hypothetical graph on the effects of aging and AD on episodic memory performance (**figure 1**).

Figure 1
Hypothetical graph illustrating episodic memory performance in aging and Alzheimer's Disease (AD).



This thesis focuses on the episodic memory processes that become impaired in aging and/or AD.

Brain structures that support episodic memory

Episodic memory is built up of different processes:

1) Encoding — Processing at the moment an event is experienced (memory acquisition), that renders it accessible for future retrieval (Brown and Craik 2000).

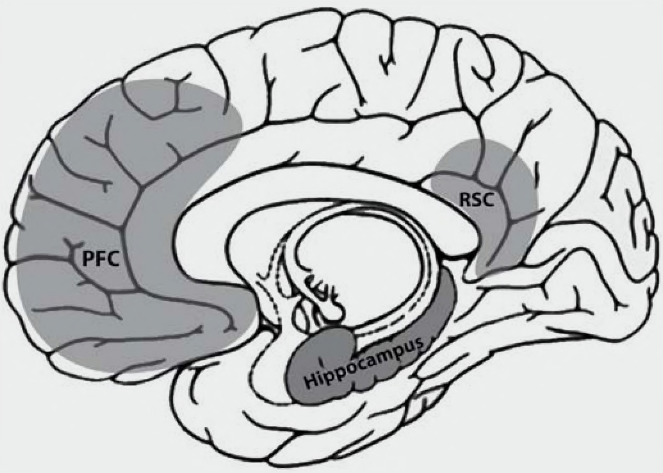
2) Consolidation — Post-acquisition stabilisation of initially fragile memory traces, ranging from the molecular/cellular level (cellular consolidation) to the regional level (systems consolidation) and from minutes to months (Dudai 2002, Dudai 2004).

3) Retrieval — Accessing of stored information by recognition (familiarity) or recall (recollection) (Baddeley 2002).

The complex nature of episodic memory is reflected by the fact that it is supported by many brain structures. However, there are three regions that are central to episodic memory, as lesions in these areas cause amnesic symptoms. These are the medial temporal lobe (MTL) with the hippocampus at its core, the prefrontal cortex (PFC) and the retrosplenial cortex (RSC; see **figure 2**), which will be described next, including their structural and functional changes observed in aging and AD.

Figure 2

The main brain structures supporting episodic memory. PFC = prefrontal cortex; RSC = retrosplenial cortex.

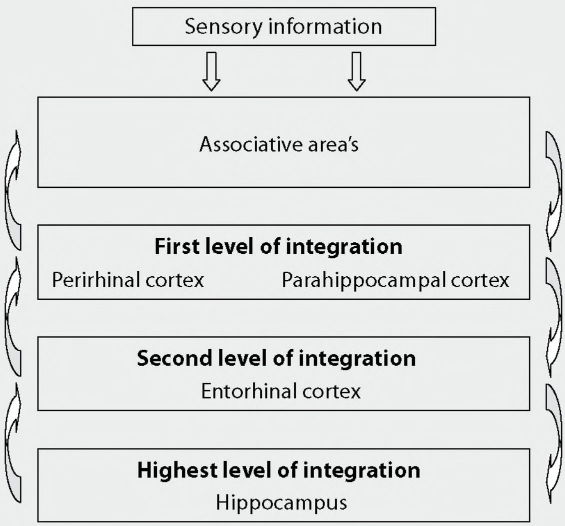


The Medial Temporal Lobe (MTL)

Lesions of the MTL cause severe amnesia, as was illustrated by patient H.M. (Milner 1970, Scoville and Milner 1957). Importantly, this amnesia is independent of the modality (e.g. visual or auditory) in which information is presented (Levy et al. 2003, Milner 1972), and does not affect perceptual abilities and intelligence (Kensinger et al. 2001, Schmolck et al. 2000, Schmolck et al. 2002). Therefore, the MTL is regarded as the main hub of episodic memory.

The MTL consists of the hippocampus and adjacent perirhinal (Brodmann area 35), entorhinal (Brodmann area 28/34) and parahippocampal cortices (Brodmann area 36) (for review, see Squire et al. 2004). Sensory information flows through associative areas to perirhinal and parahippocampal cortex to the entorhinal cortex, and from there to the hippocampus. Every connection is reciprocal, which means that information is also back-projected to the areas lower in the hierarchy (see **figure 3**).

Figure 3
The information flow to the hippocampus.



The hippocampus is where the highest level of integration (or abstraction) is achieved. Therefore, the hippocampus is able to facilitate the instantaneous storage of the "what", "where" and "when" of an event. In other words, the hippocampus is responsible for the uniqueness of episodic memories.

Finally, the hippocampus is regarded to serve as an index: it links and integrates information (memory traces) in the form of distributed neocortical representations (Marr 1971, Teyler and DiScenna 1986, Moscovitch et al. 2005, Moscovitch et al. 2006). This view has been described in more detail in a recent update of the "Hippocampal-Neocortical Interactions Theory" (Wang and Morris 2010), which states that the hippocampus does not work in isolation, but works together with cortical networks, where it is believed that long-term memory traces are stored (Osada et al. 2008).

The Prefrontal Cortex (PFC)

Within the prefrontal cortex, an important distinction can be made between the dorsolateral prefrontal cortex (DLPFC) and the (ventro) medial prefrontal cortex (vmPFC). The role of the DLPFC in this thesis is small compared to the vmPFC, and will therefore be only very briefly introduced.

The DLPFC (Brodmann areas 9/46) is part of a frontal-striatal network that supports strategic memory (for review, see Gabrieli 1998). Strategic processing (or working with memory: for instance categorically organising items) is particularly beneficial when the information to be retrieved consists of large quantities of complex information, as is often the case in daily life.

The vmPFC is a combination of the medial subset of the orbitofrontal cortex (OFC: Brodmann areas 10-14) and the ventral medial wall of the prefrontal cortex (PFC), which includes the pregenual and ventral anterior cingulate (Brodmann areas 25 and partly 24 and 32) (Bechara et al. 2000, Ongur and Price 2000). It is connected to many areas, including (somato)sensory areas, the amygdala, entorhinal cortex and hippocampus (for review, see Price 2006). These connections point to an integrative nature like the hippocampus.

The role of the vmPFC is still a topic of debate and there are many hypotheses. The coexistence of these hypotheses is a corollary of the size of the vmPFC; it is a large heterogeneous area that probably hosts several functional subregions. There are two hypotheses particularly focused on memory:

Post-retrieval monitoring (also known as the "Feeling of Rightness") (Elliott et al. 2000, Milner and Petrides 1984, Moscovitch and Winocur 2002) states that the vmPFC monitors the information retrieved and tests its veracity. Support for this hypothesis comes mainly from lesion studies, which systematically observe confabulation behaviour in patients with vmPFC damage (Curran et al. 1997, Gilboa et al. 2009, Lavoie et al. 2006, Parkin et al. 1996, Schacter et al. 1996, Verfaellie et al. 2004).

The second hypothesis states that the vmPFC takes over (with time, or consolidation) the function of the hippocampus in linking and integrating distributed neocortical representations. A role for the vmPFC in consolidation, was first indicated by the observation that lesions of the vmPFC in rodents cause a selective memory retrieval deficit for remote but not recent memories (Akirav and Maroun, 2006, Takehara et al. 2003). After that, it was demonstrated that retrieval activation in the vmPFC increases while activation of the hippocampus decreases with consolidation in rodents (Bontempi et al. 1999, Takehara-Nishiuchi and McNaughton 2008) and humans (Takashima et al. 2006, Takashima et al. 2007). In addition, sleep induces a memory-related functional connectivity between the hippocampus and the (v)mPFC (Gais et al. 2007). This functional connectivity between the vmPFC and the MTL is thought to support integration of new memories (Tse et al. 2007), and enhancement of crosstalk between these two areas can be compensatory, especially in the absence of a prior associative network, or schema (van Kesteren et al. 2010).

The fact that lesions of the (v)mPFC cause a selective retrieval deficit for remote but not recent memories (Akirav and Maroun 2006, Takehara et al. 2003), while lesions of the hippocampus can cause a retrieval deficit for recent memories (Eichenbaum 2000, Kim and Fanselow 1992, Scoville and Milner 2000, Takehara et al. 2003), suggests close interaction between the hippocampus and vmPFC during consolidation (for a review on transformation of memories to cortical networks, see Frankland and Bontempi 2005).

The Retrosplenial cortex (RSC)

The RSC (Brodmann area 29/30) is situated in the posterior cingulate region and lies immediately behind the splenium, the most posterior part of the corpus callosum (for a review, see Vann et al. 2009). It has reciprocal connections to the hippocampus, the parahippocampus and anterior thalamic nuclei on the one hand and connections to the prefrontal cortex (Brodmann areas 46,9,10, 11) on the other, besides direct input from V4. The RSC connects also to the mPFC, but through the posterior cingulate cortex just rostral to the RSC.

Lesion studies in rodents indicate the RSC supports spatial memory, like the detection of novel spatial arrangements of objects (e.g. Vann and Aggleton 2002). Human studies also point to a role in navigation and spatial memory, as patients have difficulty navigating in familiar and novel environments. It is hypothesised that the RSC serves as a short-term buffer for the translation between allocentric and egocentric representations.

Besides spatial memory deficits, patients also demonstrate impairments at acquiring information presented verbally or visually (Maguire 2001), and they have difficulty retrieving recent, but not very remote, autobiographical memories (Maguire 2001, Osawa et al. 2006, Valenstein et al. 1987). In addition, activation of the RSC is commonly observed in autobiographical memory tasks (Svoboda et al. 2006). Furthermore, activation of the RSC is related to retrieval success (Buckner and Wheeler 2001, Rugg et al. 2002).

Alzheimer's Disease (AD)

AD is a dementia syndrome named after Aloysius "Alois" Alzheimer (June 1864 - December 1915), a German psychiatrist and neuropathologist who described the symptoms of a 51-year-old patient named Mrs. Auguste Deter. Among behavioural and psychiatric problems, she suffered from impaired memory, disorientation, and language problems until she died in April 1906. Alzheimer studied her brain and published a paper describing the pathology (the so called extracellular amyloid plaques and intracellular neurofibrillary tangles) and clinical symptoms (amnesia) (Alzheimer 1907, Alzheimer 1911). In 1911, the first patients were diagnosed in the US.
AD is a neurodegenerative disorder with an insidious onset: there is a gradual build up of small day-to-day happenings that are not remembered. Patients have difficulty acquiring new information or rapidly forget information: they would for instance forget appointments, misplace objects like keys and repeat questions or stories (for a comprehensive review on AD, see Blennow et al. 2006).

AD can only be diagnosed with absolute certainty in post mortem brain tissue. In clinical practice, it is usually diagnosed using the diagnostic criteria of the National Institute of Neurologic, Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS - ADRDA; McKhann et al. 1984). Diagnosis is based on the presence of clinical symptoms and the absence of other potential causes (like depression or vascular dementia). Medical history, cognitive testing and physical examination (for instance MRI to assess cerebral atrophy, or analysis of biomarkers in the Cerebral Spinal Fluid (CSF)) are therefore crucial diagnostic tools. In research, usually the research criteria from Dubois and colleagues are used (Dubois et al. 2007), which comprise: (1) a core diagnostic criterion, namely episodic memory impairment; (2) supportive features (biomarkers), like MTL atrophy, abnormal CSF, specific metabolic pattern observed with PET or genetic predisposition (autosomal dominant mutation within the immediate family); and (3) exclusion criteria (same as in the NINCDS-ADRDA criteria). Patients should fulfill at least the core criterion and one or more of the supportive features. The research criteria from Dubois were used in the studies described in this thesis.

As AD is a progressive disorder, symptoms tend to worsen gradually and besides episodic memory, also other cognitive domains become affected, like language, visuospatial processing or executive functions. On average, the cognitive decline is about 3-4 points on the Mini-Mental State Examination (Folstein et al. 1975) per year and the average duration from diagnosis to death is 8-12 years. The disease course is divided into 7 stages, from No impairment (1), Subjective complaints (2) and Mild Cognitive Impairment (3), to Mild (4), Moderate (5), Moderate-severe (6) and Severe AD (7) according to the Global Deterioration Scale (GDS; Reisberg et al. 1982).

Nowadays, AD is a silent epidemic: due to aging of the population, the number of AD patients in The Netherlands will have increased from 190.000 now, to more than 350.000 by the year 2050 (www.alzheimer-nederland.nl). Worldwide, approximately one out of every ten elderly (older than 65) will be affected by AD. Therefore, this disorder will pose an increasing challenge to public health and elderly care systems across many nations in the world.

Effects of aging and Alzheimer's disease on the brain structures that support episodic memory

The medial temporal lobe (MTL)

The normal structural decline of the MTL with age is relatively slow, but shrinkage of the hippocampus is still estimated between 0.4 and 1.2% a year. This variability is probably caused by the fact that its decline appears to be non-linear, with atrophy restricted to old age (Raz 2005). This indicates that hippocampal degradation might not be part of "healthy aging", but is an expression of underlying pathology. The entorhinal cortex generally stays intact until very old age (Insausti et al. 1998).

The functional decline seems to contradict the mild structural decline: episodic memory is among the brain functions that suffer the most decay with aging. Elderly for instance have problems remembering lists of words (e.g. Smith 1977), stories (e.g. Pratt et al. 1989), contextual details (e.g. Park and Puglisi 1985), faces (e.g. Bartlett et al. 1989) and routes (e.g. Moffat et al. 2001, Moffat et al. 2006). Episodic memory declines "lifelong" (from around the age of 20 onwards) in a linear fashion. Contrastingly, autobiographical memory seems unchanged throughout life (Hedden and Gabrieli 2004). This might be due to the highly consolidated nature of the memory traces.

The pathophysiological processes in AD cause neuronal loss, and therefore, atrophy can be observed, starting in the MTL, in particular the entorhinal cortex and hippocampus. In fact, the entorhinal cortex is the first structure to show pathology in AD (Braak and Braak 1991). A substantial number of studies have shown that MRI measurements of hippocampal atrophy can distinguish AD from cognitively normal elderly people with 80–90% accuracy (e.g. Jagust et al. 2006), which is why hippocampal atrophy is one of AD's main biomarkers.

Episodic memory is severely impaired in AD, and seems to be an exaggeration of the deficits observed in healthy aging (Buckner 2004). Autobiographical memory also seems relatively preserved in AD, but eventually becomes impaired late in the disease course (e.g. Gilboa et al. 2005).

The prefrontal cortex (PFC)

Of all brain structures, the frontal lobe declines fastest with aging. Cross-sectional and longitudinal studies indicate a linear decline of 0.56% of total volume per year (from around the age of 20 onwards, Raz and Rodrigue 2006). White matter remains relatively preserved and declines in late life, while gray matter volume declines between 0.6 and 1.5% per year (Raz 2005).

It has been hypothesised that age-related changes to the (DL)PFC cause reduced processing speed and executive functioning, which in turn lead to a general processing deficit, particularly affecting the strategic part of episodic memory, because that requires many cognitive resources. For instance, elderly show reduced performance on tasks involving cued recall (Craik and McDowd 1987), source memory (Wegesin et al. 2000) and associative memory (Naveh-Benjamin 2000, 2003, 2004). These are all tasks that require the internal generation of strategies to guide memory.

Compared to normal aging, AD-related white matter decline in PFC does not seem accelerated, at least not in the early stage (Head et al. 2005). Also gray matter differences are mild, and metabolism stays preserved as well, but there is significant amyloid deposition in the PFC (for review, see Buckner et al. 2005).

In accordance with the structural data, the functional changes related to the PFC in AD are mild. There is some evidence that the PFC becomes disconnected from the MTL (for review, see Grady 2005), while some patients are able to recruit the (lateral) PFC during memory tasks, leading to better performance (Grady et al. 2003).

The retrosplenial cortex (RSC)

No studies have to date investigated specific structural decline of the RSC in aging, thus one has to turn to studies of the parietal cortex in general to get an indication. Decline of parietal volume in aging is far less than that of the frontal or temporal lobe, and has a rate of -0.20% per year (Raz and Rodrigue 2006). Both gray and white matter stay relatively intact and therefore, age-related structural decline of the RSC is the smallest of the neural circuit supporting episodic memory.

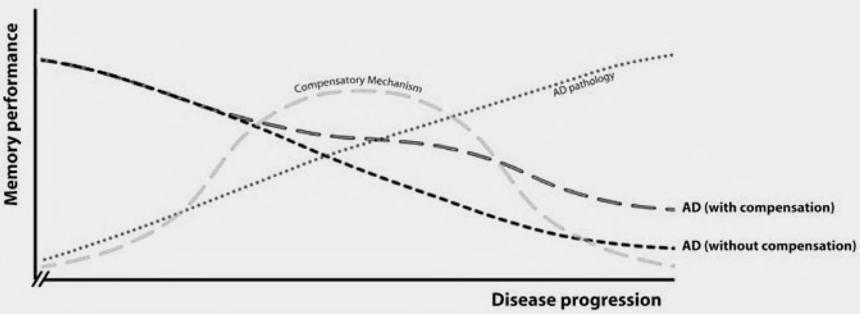
The relatively small structural decline does not accord with the age-related functional differences. For instance, aging attenuates recollection related RSC activity for words (Daselaar et al. 2006). In that same study, it was observed that aging causes functional disconnection with the hippocampus, but increased connectivity to the PFC. This data is corroborated by a working memory study by Sambataro (2010), but then with specific connectivity to the mPFC. During rest, there seems to be less connectivity between the PFC and RSC compared to young subjects (in the "default network", e.g. Damoiseaux et al. 2008).

Research surrounding structural changes of the RSC in AD is also scarce, but Scahill and colleagues (2002) observed gray matter atrophy in patients with moderate AD and patients that converted from preclinical to clinical AD. Marked hypometabolism in the RSC (as measured with 18F-fluorodoxyglucuse (FDG) PET) already in an early stage of AD (for review, see Buckner 2004). Furthermore, this decreased metabolism is correlated with amyloid deposition in that same region (Klunk et al. 2004). This indicates AD pathology also spreads to the RSC. Lastly, decreased functional connectivity between the MTL and RSC has been observed as a consequence of AD (e.g. Greicius et al. 2004).

Compensation

Structural and functional alterations in the brain do not always lead to measurable changes on the behavioural level (see **figure 4**). Cabeza and colleagues (2002) for instance observed bilateral prefrontal activation in elderly on a memory retrieval task, while young participants that performed equally well displayed activation on the right side only. Low performing elderly also displayed only right-lateralised activation. These data indicate that the normal performing elderly recruited the contralateral homologous brain area as compensation, and this effect became subsequently known as Hemispheric Asymmetry Reduction in Older adults (or HAROLD; Cabeza 2002). The same effect has been observed in the hippocampus for autobiographical memory retrieval (Maguire and Frith 2003) and in the inferior frontal gyrus and anterior prefrontal cortex for successful memory encoding (Morcom et al. 2003).

Figure 4
Hypothetical graph illustrating the beneficial effect of compensation on episodic memory performance in Alzheimer's Disease (AD) Hypothetical graph illustrating episodic memory performance in aging and Alzheimer's Disease (AD).



Besides recruitment of other brain areas, compensation is also often displayed as a general overactivation that is correlated with good performance, regional volume, or is correlated with declining activation in impaired regions (Reuter-Lorenz and Lustig 2005). Below is an overview of the interpretation following from observed activation and behavioural effects (**table 1**).

Table 1
Interpretation of brain activation differences and their relation to behavioural performance.

Brain Activation	Behavioural Performance	Correlation between activation & performance?	Interpretation
More	Equal	Yes	Compensation
		No	De-differentiation/ non-selective recruitment
More	Worse	Yes	Compensation
		No	Impairment: inefficiency inhibition failure different/ wrong strategy non-selective recruitment
Less	Worse	Yes/No	Impairment: inefficiency inhibition failure different/ wrong strategy

In the (very) early stages of AD, patients are still able to compensate during episodic memory tasks, for instance by recruitment of the lateral PFC (Grady et al. 2003) or the temporoparietal cortex (Becker et al. 1996, Stern et al. 2000), keeping normal cognitive performance despite the changing neural substrate.

In conclusion, we know now that aging and AD affects episodic memory, for instance by changing the structure and functionality of the main brain regions that support this process: the medial temporal lobe (MTL), the prefrontal cortex (PFC) and the retrosplenial cortex (RSC). Next to impairment, these areas can also show signs of compensation.

Structural and functional changes, as well as compensatory processes, can ideally be measured with (functional) MRI, which is the main research method of the studies in this thesis. Therefore, detection of compensatory processes early in the disease course with fMRI, has a potential role as biomarker that can speed up diagnosis and opens the door to new interventions. This is the reason this thesis focuses on the effects of aging and AD on the neural correlates of episodic memory.

Thesis outline

In this thesis, the effects of aging and AD on the neural correlates of different episodic memory processes is investigated. The first two chapters (chapters 2 and 3) focus on aging, in particular with respect to spatial (associative) memory. The remaining two chapters investigate AD (chapters 4 and 5), focussing on autobiographical, semantic and recognition memory.

Aging

Chapter 2 presents the neural correlates of spatial memory encoding and retrieval, in a task using routes through virtual houses. In chapter 3, we report a study on the effect of environmental support during encoding on retrieval of object place associations. Poor environmental support places a higher demand on cognitive resources and requires more self-initiated (and therefore strategic) processing. Since aging is accompanied by a resource deficit, a manipulation in environmental support will therefore affect the way elderly approach a memory task.

Alzheimer's disease (AD)

In chapter 4, autobiographical memory retrieval is compared with semantic memory retrieval in healthy elderly and AD patients, because semantisation of autobiographical memory is enhanced in AD patients. This chapter indicates an important share of the vmPFC in autobiographical memory retrieval in AD patients. Therefore, chapter 5 further explores structural and functional integrity of the hippocampus and vmPFC in the episodic memory network, using multiple measures: (1) recognition memory performance; (2) brain morphology (voxel-based morphometry); (3) neural processing related to successful memory retrieval (event-related fMRI); and (4) functional connectivity between the hippocampus and vmPFC (resting-state fMRI).

References

Akirav I, Maroun M. Ventromedial prefrontal cortex is obligatory for consolidation and reconsolidation of object recognition memory. Cereb Cortex 2006; 16: 1759-65.

Alzheimer A. Über eine eigenartige erkrankung der Hirnrinde. Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin 1907; 64: 146-148.

Alzheimer A. Über eigenartige Krankheitsfälle des späteren Alters. Zeitschrift für die gesamte Neurologie und Psychiatrie 1911; 4: 356-385.

Baddeley AD. The psychology of memory. In: Baddeley AD, Kopelman MD, Wilson BA, editors. The handbook of memory disorders. Chichester: John Wiley & Sons Ltd; 2002. p. 3-15.

Bartlett JC, Leslie JE, Tubbs A, Fulton A. Aging and memory for pictures of faces. Psychol Aging 1989; 4: 276-283.

Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. Cereb Cortex 2000; 10: 295-307.

Becker JT, Mintun MA, Aleva K, Wiseman MB, Nichols T, Dekosky ST. Compensatory reallocation of brain resources supporting verbal episodic memory in Alzheimer's disease. Neurology 1996; 46: 692-700.

Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet 2006; 368: 387-403.

Bontempi B, Laurent-Demir C, Destrade C, Jaffard R. Time-dependent reorganization of brain circuitry underlying long-term memory storage. Nature 1999; 400: 671-5.

Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991; 82: 239-259.

Brown SC, Craik FIM. Encoding and retrieval of information. In: Tulving E, Craik FIM, editors. The Oxford handbook of memory. New York, NY: Oxford University Press; 2000. p. 93-107.

Buckner RL. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 2004; 44: 195-208.

Buckner RL, Snyder AZ, Shannon BJ *et al.* Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci 2005; 25: 7709-17.

Buckner RL, Wheeler ME. The cognitive neuroscience of remembering. Nat Rev Neurosci 2001; 2: 624-634.

Cabeza R. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging 2002; 17: 85-100.

Craik FIM, McDowd JM. Age Differences in Recall and Recognition. [Article]. Journal of Experimental Psychology: Learning, Memory, & Cognition 1987; 474-479.

Curran T, Schacter DL, Norman KA, Galluccio L. False recognition after a right frontal lobe infarction: memory for general and specific information. Neuropsychologia 1997; 35: 1035-1049.

Damoiseaux JS, Beckmann CF, Arigita EJ *et al.* Reduced resting-state brain activity in the "default network" in normal aging. Cereb Cortex 2008; 18: 1856-1864.

Daselaar SM, Fleck MS, Dobbins IG, Madden DJ, Cabeza R. Effects of healthy aging on hippocampal and rhinal memory functions: an event-related fMRI study. Cereb Cortex 2006; 16: 1771-1782.

Dubois B, Feldman HH, Jacova C *et al.* Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007; 6: 734-46.

Dudai Y. Molecular bases of long-term memories: a question of persistence. Curr Opin Neurobiol 2002; 12: 211-216.

Dudai Y. The neurobiology of consolidations, or, how stable is the engram? Annu Rev Psychol 2004; 55: 51-86.

Eichenbaum H. A cortical-hippocampal system for declarative memory. Nat Rev Neurosci 2000; 1: 41-50.

Elliott R, Dolan RJ, Frith CD. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cereb Cortex 2000; 10: 308-317.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-98.

Frankland PW, Bontempi B. The organization of recent and remote memories. Nat Rev Neurosci 2005; 6: 119-130.

Gabrieli JDE. Cognitive neuroscience of human memory. Annual Review of Psychology 1998; 49: 87-115.

Gais S, Albouy G, Boly M *et al.* Sleep transforms the cerebral trace of declarative memories. Proc Natl Acad Sci U S A 2007; 104: 18778-18783.

Gilboa A, Alain C, He Y, Stuss DT, Moscovitch M. Ventromedial prefrontal cortex lesions produce early functional alterations during remote memory retrieval. J Neurosci 2009; 29: 4871-4881.

Gilboa A, Ramirez J, Kohler S, Westmacott R, Black SE, Moscovitch M. Retrieval of autobiographical memory in Alzheimer's disease: relation to volumes of medial temporal lobe and other structures. Hippocampus 2005; 15: 535-550.

Grady CL. Functional connectivity during memory tasks. In: Cabeza R, Nyberg L, Park D, editors. Cognitive neuroscience of aging; linking cognitive and cerebral aging. New York: Oxford University Press; 2005. p. 286-308.

Grady CL, McIntosh AR, Beig S, Keightley ML, Burian H, Black SE. Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. J Neurosci 2003; 23: 986-993.

Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci U S A 2004; 101: 4637-4642.

Head D, Snyder AZ, Girton LE, Morris JC, Buckner RL. Frontal-hippocampal double dissociation between normal aging and Alzheimer's disease. Cereb Cortex 2005; 15: 732-739.

Hedden T, Gabrieli JD. Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev Neurosci 2004; 5: 87-96.

Insausti R, Juottonen K, Soininen H *et al.* MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. AJNR Am J Neuroradiol 1998; 19: 659-671.

Jagust W, Gitcho A, Sun F, Kuczynski B, Mungas D, Haan M. Brain imaging evidence of preclinical Alzheimer's disease in normal aging. Ann Neurol 2006; 59: 673-681.

Kensinger EA, Ullman MT, Corkin S. Bilateral medial temporal lobe damage does not affect lexical or grammatical processing: evidence from amnesic patient H.M. Hippocampus 2001; 11: 347-360.

Kim JJ, Fanselow MS. Modality-specific retrograde amnesia of fear. Science 1992; 256: 675-677.

Klunk WE, Engler H, Nordberg A *et al.* Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 2004; 55: 306-319.

Lavoie DJ, Willoughby L, Faulkner K. Frontal lobe dysfunction and false memory susceptibility in older adults. Exp Aging Res 2006; 32: 1-21.

Levy DA, Manns JR, Hopkins RO, Gold JJ, Broadbent NJ, Squire LR. Impaired visual and odor recognition memory span in patients with hippocampal lesions. Learn Mem 2003; 10: 531-536.

Maguire EA. The retrosplenial contribution to human navigation: a review of lesion and neuroimaging findings. Scand J Psychol 2001; 42: 225-238.

Maguire EA, Frith CD. Aging affects the engagement of the hippocampus during autobiographical memory retrieval. Brain 2003; 126: 1511-1523.

Marr D. Simple memory: a theory for archicortex. Philos Trans R Soc Lond B Biol Sci 1971; 262: 23-81.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34: 939-944.

Milner B. Memory and the medial temporal regions of the brain. In: Pribram KH, Broadbent DE, editors. Biology of memory. San Diego, CA: Academic Press; 1970. p. 29-50.

Milner B. Disorders of learning and memory after temporal lobe lesions in man. Clin Neurosurg 1972; 19: 421-446.

Milner B, Petrides M. Behavioural effects of frontal-lobe lesions in man. Trends in Neurosciences 1984; 7: 403-407.

Moffat SD, Elkins W, Resnick SM. Age differences in the neural systems supporting human allocentric spatial navigation. Neurobiol Aging 2006; 27: 965-972.

Moffat SD, Zonderman AB, Resnick SM. Age differences in spatial memory in a virtual environment navigation task. Neurobiol Aging 2001; 22: 787-796.

Morcom AM, Good CD, Frackowiak RS, Rugg MD. Age effects on the neural correlates of successful memory encoding. Brain 2003; 126: 213-229.

Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum RS. The cognitive neuroscience of remote episodic, semantic and spatial memory. Curr Opin Neurobiol 2006; 16: 179-190.

Moscovitch M, Rosenbaum RS, Gilboa A *et al.* Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. J Anat 2005; 207: 35-66.

Moscovitch M, Winocur G. The frontal cortex and working with memory. In: Stuss DT, Knight R, editors. Principles of frontal lobe function. New York: Oxford University Press; 2002. p. 188-209.

Naveh-Benjamin M. Adult age differences in memory performance: tests of an associative deficit hypothesis. J Exp Psychol Learn Mem Cogn 2000; 26: 1170-1187.

Naveh-Benjamin M, Guez J, Kilb A, Reedy S. The associative memory deficit of older adults: further support using face-name associations. Psychol Aging 2004; 19: 541-546.

Naveh-Benjamin M, Hussain Z, Guez J, Bar-On M. Adult age differences in episodic memory: further support for an associative-deficit hypothesis. J Exp Psychol Learn Mem Cogn 2003; 29: 826-837.

Ongur D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cereb Cortex 2000; 10: 206-219.

Osada T, Adachi Y, Kimura HM, Miyashita Y. Towards understanding of the cortical network underlying associative memory. Philos Trans R Soc Lond B Biol Sci 2008; 363: 2187-2199.

Osawa A, Maeshima S, Kubo K, Itakura T. Neuropsychological deficits associated with a tumour in the posterior corpus callosum: a report of two cases. Brain Inj 2006; 20: 673-676.

Park DC, Puglisi JT. Older adults' memory for the color of pictures and words. J Gerontol 1985; 40: 198-204.

Parkin AJ, Bindschaedler C, Harsent L, Metzler C. Pathological false alarm rates following damage to the left frontal cortex. Brain Cogn 1996; 32: 14-27.

Pratt MW, Boyes C, Robins S, Manchester J. Telling tales: Aging, working memory, and the narrative cohesion of story retellings. Developmental Psychology 1989; 25: 628-635.

Price JL. Connections of orbital cortex. In: Zald DH, Rauch SL, editors. The orbitofrontal cortex. New York: Oxford University Press; 2006.

Raz N. The aging brain observed in vivo: differential changes and their modifiers. In: Cabeza R, Nyberg L, Park D, editors. Cognitive neuroscience of aging; linking cognitive and cerebral aging. New York: Oxford University Press; 2005. p. 19-57.

Raz N, Rodrigue KM. Differential aging of the brain: Patterns, cognitive correlates and modifiers. Neuroscience & Biobehavioral Reviews 2006; 30: 730-748.

Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry 1982; 139: 1136-1139.

Reuter-Lorenz PA, Lustig C. Brain aging: reorganizing discoveries about the aging mind. Curr Opin Neurobiol 2005; 15: 245-251.

Rugg MD, Otten LJ, Henson RN. The neural basis of episodic memory: evidence from functional neuroimaging. Philos Trans R Soc Lond B Biol Sci 2002; 357: 1097-1110.

Sambataro F, Murty VP, Callicott JH *et al.* Age-related alterations in default mode network: impact on working memory performance. Neurobiol Aging 2010; 31: 839-852.

Scahill RI, Schott JM, Stevens JM, Rossor MN, Fox NC. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. Proc Natl Acad Sci U S A 2002; 99: 4703-4707.

Schacter DL, Curran T, Galluccio L, Milberg WP, Bates JF. False recognition and the right frontal lobe: a case study. Neuropsychologia 1996; 34: 793-808.

Schmolck H, Kensinger EA, Corkin S, Squire LR. Semantic knowledge in patient H.M. and other patients with bilateral medial and lateral temporal lobe lesions. Hippocampus 2002; 12: 520-533.

Schmolck H, Stefanacci L, Squire LR. Detection and explanation of sentence ambiguity are unaffected by hippocampal lesions but are impaired by larger temporal lobe lesions. Hippocampus 2000; 10: 759-770.

Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neurol Neurosurg Psychiatry 1957; 20: 11-21.

Scoville WB, Milner B. Loss of Recent Memory After Bilateral Hippocampal Lesions. J Neuropsychiatry Clin Neurosci 2000; 12: 103-10a.

Smith AD. Adult age differences in cued recall. Developmental Psychology 1977; 326-331.

Squire LR, Stark CE, Clark RE. The medial temporal lobe. Annu Rev Neurosci 2004; 27: 279-306.

Stern Y, Moeller JR, Anderson KE *et al.* Different brain networks mediate task performance in normal aging and AD: defining compensation. Neurology 2000; 55: 1291-1297.

Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. Neuropsychologia 2006; 44: 2189-208.

Takashima A, Nieuwenhuis IL, Rijpkema M, Petersson KM, Jensen O, Fernandez G. Memory trace stabilization leads to large-scale changes in the retrieval network: a functional MRI study on associative memory. Learn Mem 2007; 14: 472-479.

Takashima A, Petersson KM, Rutters F *et al.* Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Natl Acad Sci U S A 2006; 103: 756-61.

Takehara K, Kawahara S, Kirino Y. Time-dependent reorganization of the brain components underlying memory retention in trace eyeblink conditioning. J Neurosci 2003; 23: 9897-905.

Takehara-Nishiuchi K, McNaughton BL. Spontaneous Changes of Neocortical Code for Associative Memory During Consolidation. Science 2008; 322: 960-963.

Teyler TJ, DiScenna P. The hippocampal memory indexing theory. Behav Neurosci 1986; 100: 147-154.

Tse D, Langston RF, Kakeyama M *et al.* Schemas and memory consolidation. Science 2007; 316: 76-82.

Tulving E. Episodic memory: from mind to brain. Annu Rev Psychol 2002; 53: 1-25.

Valenstein E, Bowers D, Verfaellie M, Heilman KM, Day A, Watson RT. Retrosplenial amnesia. Brain 1987; 110 (Pt 6): 1631-1646.

van Kesteren MT, Fernandez G, Norris DG, Hermans EJ. Persistent schema-dependent hippocampal-neocortical connectivity during memory encoding and postencoding rest in humans. Proc Natl Acad Sci U S A 2010; 107: 7550-7555.

Vann SD, Aggleton JP. Extensive cytotoxic lesions of the rat retrosplenial cortex reveal consistent deficits on tasks that tax allocentric spatial memory. Behav Neurosci 2002; 116: 85-94.

Vann SD, Aggleton JP, Maguire EA. What does the retrosplenial cortex do? Nat Rev Neurosci 2009; 10: 792-802.

Verfaellie M, Rapcsak SZ, Keane MM, Alexander MP. Elevated false recognition in patients with frontal lobe damage is neither a general nor a unitary phenomenon. Neuropsychology 2004; 18: 94-103.

Wang SH, Morris RGM. Hippocampal-Neocortical Interactions in Memory Formation, Consolidation, and Reconsolidation. Annual Review of Psychology 2010; 61: 49-79.

Wegesin DJ, Jacobs DM, Zubin NR, Ventura PR, Stern Y. Source memory and encoding strategy in normal aging. J Clin Exp Neuropsychol 2000; 22: 455-464.

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2

Chapter

Age differences in neural correlates of route encoding and route recognition

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Abstract

Spatial memory deficits are core features of aging-related changes in cognitive abilities. The neural correlates of these deficits are largely unknown. In the present study, we investigated the neural underpinnings of age-related differences in spatial memory by functional MRI, using a navigational memory task with route encoding and route recognition conditions. We investigated 20 healthy young (18-29 years) and 20 healthy old adults (53-78 years) in a random effects analysis. Old subjects showed slightly poorer performance than young subjects. Compared to the control condition, route encoding and route recognition showed activation of the dorsal and ventral visual processing streams and the frontal eye fields in both groups of subjects. Compared to old adults, young subjects showed during route encoding stronger activations in the dorsal and the ventral visual processing stream (supramarginal gyrus and posterior fusiform/ parahippocampal areas). In addition, young subjects showed weaker anterior parahippocampal activity during route recognition compared to the old group. In contrast, old compared to young subjects showed less suppressed activity in the left perisylvian region and the anterior cingulate cortex during route encoding. Our findings suggest that age-related navigational memory deficits might be caused by less effective route encoding based on reduced posterior fusiform/ parahippocampal and parietal functionality combined with diminished inhibition of perisylvian and anterior cingulate cortices correlated with less effective suppression of task irrelevant information. In contrast, age-differences in neural correlates of route recognition seem to be rather subtle. Old subjects might show a diminished familiarity signal during route recognition in the anterior parahippocampal region.

Introduction

Deficits in spatial and navigational memory are important components of aging-related changes in cognitive abilities (for review see Kirasic, 2001). It is common that elderly individuals not only avoid unfamiliar routes and places due to self-perceived deficits in navigation (Burns 1999), they also have measurable deficits in place and route learning as assessed in real- and virtual reality environments (Kirasic, 1991; Kirasic et al., 1992; Wilkniss et al., 1997; Moffat et al., 2001; Moffat & Resnick 2002). Moreover, navigational memory deficits are an important marker of early dementia and thus relevant for early diagnosis (Morris, 1993). Thus, elderly adults encounter more difficulty in learning and remembering new routes in novel environments as compared to younger adults. However, the neural correlates of these age-related differences in route encoding and route recognition are unknown. Moreover, it is unknown whether an encoding or a retrieval deficit causes navigational deficits in old age.

In young subjects, several imaging studies have identified brain structures involved in the encoding of new and recognition of familiar environments (for review, see Burgess et al., 2002). Encoding is consistently accompanied by activation of the dorsal visual pathway reaching the parietal lobe and the ventral visual pathway, extending into the medial temporal lobe (MTL). The effectiveness of navigational encoding seems to be positively correlated with inferior and medial temporal activity (Aguirre et al., 1996; Aguirre and D'Esposito, 1997; Hartley et al., 2003; Iaria et al., 2003; Maguire et al., 1998a,b). The general relation between temporal activity and effective encoding is also well supported by studies using the subsequent memory effect, which show greater posterior fusiform/parahippocampal activity for later remembered as compared to later forgotten pictures depicting large-scale spatial layouts (Brewer et al., 1998; Kirchhoff et al., 2000, Weis et al., 2004).

There is considerable overlap in brain activation observed during encoding and retrieval of navigational information. Nevertheless, recognition of learned spatial environments in a route recognition task is often accompanied by more prefrontal activations compared to encoding, including activations of the anterior cingulate cortex as well as the pre- and supplementary motor cortices (Burgess et al., 2002).

Although no functional neuroimaging study has yet investigated the neural correlates of age-related deficits in navigational memory, there are several studies that tackle age-related declarative memory deficits in general. The most consistent finding reported in these studies include a reduced encoding related inferior and medial temporal activity in older as compared to younger subjects (e.g. Grady et al., 1995; Daselaar et al., 2003; Morcom et al., 2003; Schiavetto et al., 2002). In addition, older subjects appear to recruit additionally other brain regions, predominately in the prefrontal cortex. The recruitment of frontal regions together with the relatively diminished responses observed in the temporal lobe and other posterior regions, including the parietal cortex, is sometimes referred to as the posterior – anterior shift (Grady et al., 2003). It has been suggested that with increasing age additional cognitive resources involving executive and organizational functions are utilized instead or in complement to the perceptually based processes engaged by younger subjects. The prefrontal activations in older subjects are often less asymmetric than in young subjects, leading Cabeza (2002) to formulate the so-called HAROLD model (Hemispheric Asymmetry Reduction in Older adults). Such reductions in asymmetry have most consistently been found in high performing older adults (Cabeza et al., 2002). Therefore, the recruitment of the homologue prefrontal region in the contralateral hemisphere has been regarded as a mechanism for compensating age-related deficits in other brain regions including the temporal lobe (Cabeza et al., 2002; Daselaar et al., 2003; Dolcos et al., 2002; Grady and Craik, 2000; Logan et al., 2002). In contrast, in some circumstances, under-recruitment of frontal regions has also been observed in elderly, perhaps indicating that elderly might be less likely to self-initiate the most effective strategy for solving a given task (Cabeza et al., 1997; Grady et al., 1995; Logan et al., 2002).

Summing up the current status, older adults often show a navigational memory deficit, the neural correlates of route encoding and recognition are well studied in young subjects, and studies comparing brain activity related to mnemonic operations between younger and older adults have found consistent differences. However, the neural correlates of age-related deficits in navigational memory are, to our knowledge, yet unstudied. To tackle this issue, we investigated 20 elderly and 20 young healthy subjects by fMRI while they performed a virtual reality spatial memory task including route encoding and route recognition conditions.

Materials and methods

Participants

Forty healthy volunteers participated in the study (20 young subjects, 10 female; mean age = 23 years, SD = 2.8, range 18 - 29; 20 old subjects, 10 female; mean age = 63 years, SD = 7.2, range 53 – 78). All but two young and two old subjects were right-handed as indexed by an Edinburgh handedness index of ≥ 90 (Oldfield, 1971). The mean number of years of formal education was 16 (SD = 2.0) for old and 16 (SD = 0.4) for young subjects. Dutch was the first language in all subjects. All subjects were high functioning, mostly university educated, autonomous community dwellers. The older subjects, whilst mostly retired, were all active in cultural pursuits, continuing education or with responsibilities in various associations. All subjects were pre-screened and none of them used medication regularly, had a history of drug abuse, head trauma, or a medical condition that could affect cerebral blood flow (e.g. high blood pressure, diabetes, thyroid dysfunction). All subjects had normal or corrected-to-normal vision. The structural MRI investigations (cf., below) did not show any evidence for anatomical abnormalities atypical for the age. All subjects gave written informed consent according to the Declaration of Helsinki and the local medical ethics committee approved the study.

Stimulus material

We constructed 16 video sequences of ground-level first-person indoor routes through virtual environments each showing a different furnished home and lasting 31s using Traumhaus Designer 4.0 software (www.databecker.de). The homes were approximately of the same size and similar topology, that is, they contained the same number of rooms, furniture and other items of daily life. Fourteen sequences were used for the actual fMRI experiment and two sequences for the initial, pre-scan training session. Each video sequence depicts a fixed route through the different rooms of the homes and included five decision points (i.e., intersections). Two arrowheads, indicating left, right, or straight-ahead, appeared at every decision point for 2.5 s accompanied by a freeze of the video sequence for 2 s. In the route encoding condition one arrowhead was yellow (predicting the direction where the "travel" will go) and the other red. During the route recognition condition, both arrowheads were red. The interval between each decision point lasted 3.5 s. For the control task, one additional virtual environment was constructed depicting an empty, straight hallway. Here, the video sequence showed the same straight 'walk' and two arrowheads at the end of the hallway (one in yellow and one in red) for five times. The timing of this control video sequence was identical to the other sequences described.

Experimental procedure

The experiment included four conditions: route encoding, visuo-motor control, rest, and route recognition. Each conditions-cycle started with a route encoding condition and ended with a route recognition condition, with the order of the control and rest condition randomly changing over cycles. Before going into the scanner, subjects practiced the task in two cycles with virtual homes not used during the experiment. In the scanner, video sequences were presented by a computer using ERTS software (www.erts.de) for stimulus presentation and response recording. Stimuli were back-projected via an LCD-projector onto a translucent screen, which subjects viewed through a mirror mounted at the head coil. Subjects responded with an optical button device held in their dominant hand, and a computer interfaced with the optical switch recorded these responses. Altogether the experiment consisted of 14 cycles, separated into two runs of seven cycles each. Across subjects, we used two versions of the experiment differing in the order of cycles only. The subject's head was immobilized using a vacuum cushion to reduce motion artifacts.

Route encoding: While the subjects viewed a video sequence of a virtual home, they were instructed to remember the directions taken at each of the five decision points (left, right, straight ahead) and to press the respective button on the button-box to confirm the direction indicated by the yellow arrowhead and subsequently taken by the video sequence. Each cycle started by indicating to the subject that a new house had to be learned.

Visuo-motor control: Subjects 'traveled' repeatedly along the same empty hallway. When they saw the yellow and the red arrowhead at the end of the hallway, they were instructed to press the button assigned to the direction indicated by the yellow arrowhead.

Rest: During the rest period the display showed a white, central fixation cross on a black background and no response was required. Subjects were instructed to fixate and concentrate on scanner noise.

Route recognition: Subjects saw the same video sequence as shown previously during the learning condition of the same cycle. They were instructed to indicate by appropriate button-press as accurate as possible the correct of the two alternative directions indicated by two red arrowheads at each decision point. If the subject made an incorrect response, the video went on with the predetermined sequence.

While the contrasts between route encoding and visuo-motor control as well as route recognition and visuo-motor control are assumed to show a comprehensive, less specific picture of brain regions involved in a navigational memory task, the two contrasts between route encoding and recognition are assumed to delineate specifically the formation of navigational memories and their retrieval.

This easy navigational task has three major advantages for the purpose of our study: First, we avoid large performance differences between young and old subjects, enabling us to relate age differences to differences in brain operations and not performance, Second, we avoid free navigation with a joy-stick and thus difficult motor responses that would be much easier for young subjects who have often extensive experiences with computer games. Third, we avoid a "semantic" strategy, in which subjects remember the order of responses left, right and straight ahead, because such a strategy is much more difficult than a true navigational strategy due to interference by the large number of repetitions of just three possible responses (70 responses).

MRI Data Acquisition

During MRI scanning whole head T2*-weighted EPI-BOLD fMRI data were acquired with a Siemens Sonata 1.5T MR-scanner using an interleaved slice acquisition EPI sequence (volume TR = 1.93 s, TE = 30 ms, 90 degree flip-angle, 28 axial slices aligned with the AC-PC plane, slice-matrix size = 64 x 64, slice thickness = 3.5 mm, slice gap = 0.5 mm, FOV = 224 mm, isotropic voxel-size = 3.5x3.5x3.5 mm) in a blocked design. For the structural high-resolution MR image volume a T1-weighted MP-RAGE sequence was used (volume TR = 2250 ms, TE = 3.93 ms, 15 degree flip-angle, 176 sagittal slices, slice-matrix size = 256 x 256, slice thickness = 1 mm, slice gap = 0 mm, voxel-size = 1x1x1 mm).

MR Image Pre-processing and Statistical Analysis

Image pre-processing and statistical analysis was performed using the SPM99 software (www.fil.ion.ucl.ac.uk). The functional EPI-BOLD images were realigned and the subject-mean functional MR images were co-registered with the corresponding structural MR images using mutual information optimization. These were subsequently spatially normalized (i.e., the normalization transformations were generated from the structural MR images and applied to the functional MR images) and transformed into a common approximate Talairach space (Talairach and Tournoux, 1988), as defined by the SPM99 MNI T1 template, and finally spatially filtered by convolving the functional image volumes with an isotropic 3D spatial Gaussian filter kernel (8 mm FWHM). The fMRI data was proportionally scaled to account for global effects and analyzed statistically using the general linear model and statistical parametric mapping (Friston et al., 1995). The linear model included convolved explanatory variables (regressors), modeling the encoding, the retrieval, and baseline conditions using boxcar regressors. The explanatory variables were temporally convolved with the canonical hemodynamic response function. In addition, the linear model included the session/subject-effects, and a temporal high-pass filter to account for various low-frequency effects (e.g., related to different physiological effects such as heart-rate and respiration, and slow MR-scanner drifts). In order to account for temporal autocorrelation, the fMRI data were convolved with a Gaussian (FWHM = 4s) temporal kernel, and effective degrees of freedom estimated (Worsley and Friston, 1995). In the statistical analysis, for each subject relevant contrasts corresponding to null-hypotheses were used to generate statistic images, SPM[T]. These were then subjected to a second-level random effects analysis. Results from the random effects analyses were thresholded at $T = 3.11$ ($P = 0.001$, uncorrected) and the cluster size was used as the test statistic. Only clusters significant at $P < 0.1$ (corrected for multiple non-independent comparisons based on the theory of differentiable 3D stationary random field theory (Adler, 1981; Worsley et al., 1996)) are described. The significant clusters were resolved into peak-height of local maxima and only significant local maxima, $P < 0.05$ (corrected for multiple non-independent comparisons based on the false discovery rate (Genovese et al., 2002)) are reported. The terms of activation and deactivation are used as synonyms for a relative increase and decrease in BOLD signal, respectively.

Results

Behavioral results

The subject performance during route recognition was well above chance level (50%) in both groups (young: mean correct = 79.5%, SD = 12.0, t_{19} = 11.0, P < 0.0001; old: mean correct = 73.3%, SD = 16.8, t_{19} = 6.2, P < 0.0001). Young subjects performed slightly but significantly better than old subjects (t_{38} = 1.3, P < 0.05).

MRI results

Route encoding versus visuo-motor control condition

In young and old subjects, learning routes through unfamiliar virtual environments significantly activated relative to the visuo-motor control condition distributed regions in the parietal, occipital and inferior temporal lobes (**figure 1**). We also observed additional prefrontal activations, centered on the frontal eye fields. Overall, both groups of subjects showed a similar pattern of activation in route encoding versus the visuo-motor control condition. However, by visual inspection it appears that the activation related to the dorsal and ventral processing streams are stronger in the young as compared to the old subjects (**figure 1**). While the frontal eye field activation appears small and slightly right lateralized in the old subjects, the young subjects show a more extended and more symmetric activation of the frontal eye fields in both hemispheres. These apparent differences were confirmed in a second level statistical comparison of BOLD signal intensity differences in young and old subjects (**figure 2, table 1**). In this analysis we revealed that young subjects showed larger BOLD signal intensity differences between the route encoding condition and the visuo-motor control condition than old subjects in the bilateral superior parietal (BA 7), bilateral posterior fusiform/parahippocampal area (BA 19/37), left inferior occipital region (BA 17/18) and the left frontal eye field (BA 6). The reverse comparison revealed that the older subjects showed larger BOLD signal intensity differences between the route encoding condition and the visuo-motor control condition than young in extended bilateral regions including perisylvian BA 22/40, precuneus/ posterior cingulate (BA 23/31), anterior cingulate (BA 24/32) and medial superior frontal areas (BA 10). However, all of these relative activations in the old subjects represent smaller or missing reductions relative to the baseline provided by the visuo-motor control condition.

Figure 1
Brain regions that show greater activity in route encoding than control and route recognition than control displayed separately for old and young subjects.
Images here and in the following are thresholded at P = 0.001; L = Left, R = Right.

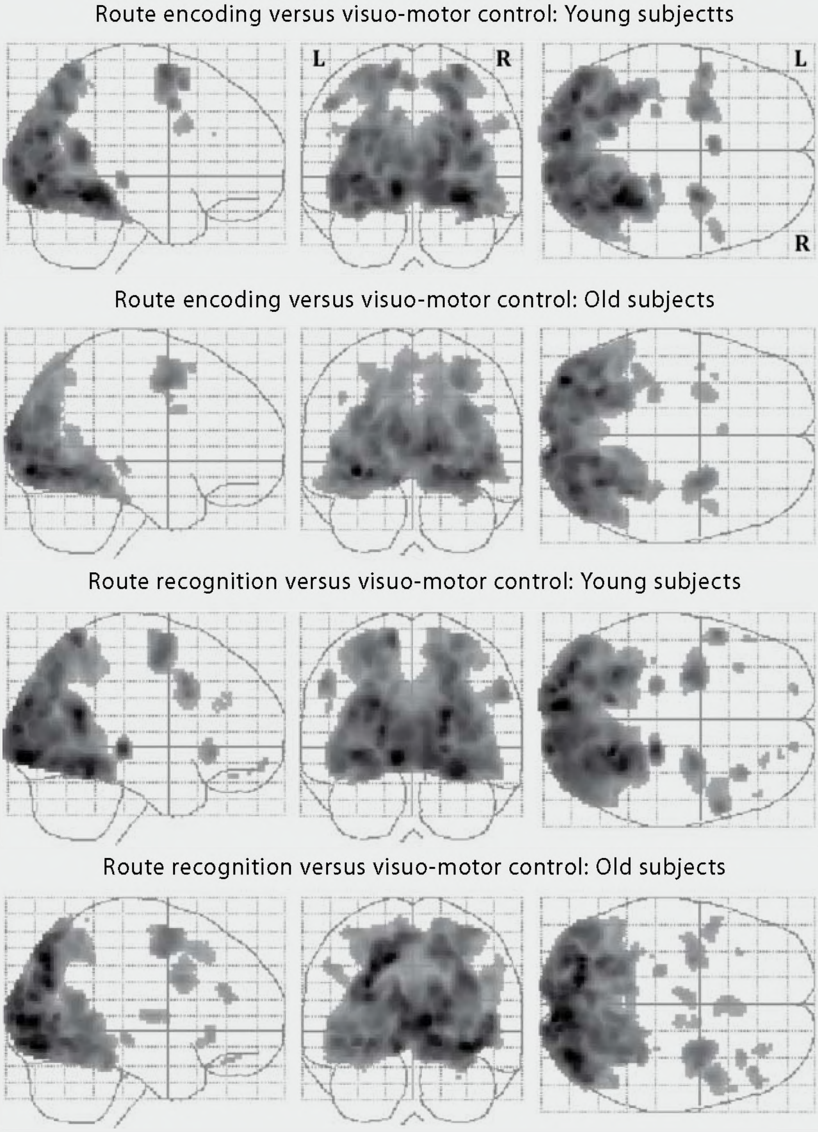


Figure 2
Brain regions that show relatively greater activity in young subjects as compared to old subjects and vice versa for the contrasts route encoding versus control and route recognition versus control.

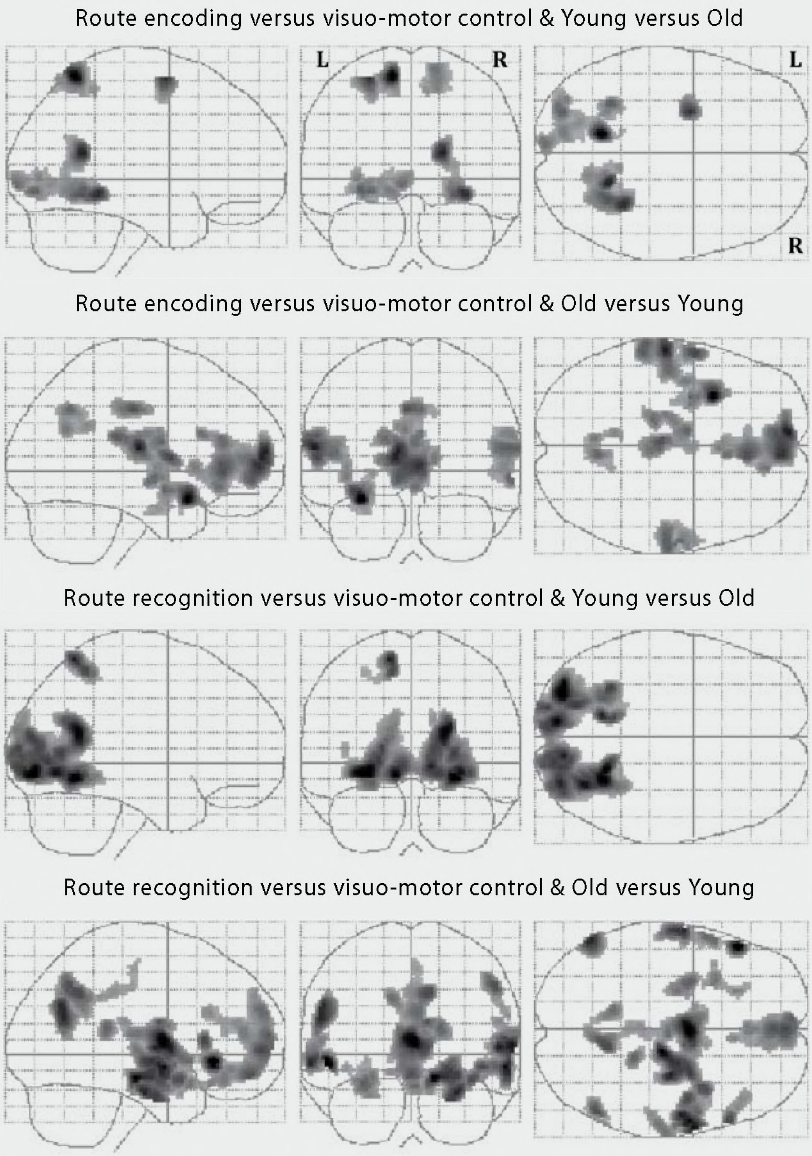


Table 1
Interpretation of brain activation differences and their relation to behavioural performance.

Region Brodmann's area	Cluster P-value	Z-score	Voxel P-value	[x y z]		
YOUNG vs. OLD						
Right superior parietal region	0.004					
BA 7		4.16	0.008	16	-56	66
"		3.91	0.015	16	-58	56
"		3.84	0.017	14	-66	60
Left superior parietal region	0.003					
BA 7		5.88	<0.001	-12	-58	64
"		3.22	0.050	-22	-72	54
"		3.22	0.050	-12	-46	58
Right fusiform region	< 0.001					
BA 37		5.20	0.001	32	-44	-8
BA 19/37		4.68	0.002	30	-54	-10
Left fusiform region	0.055					
BA 37		4.51	0.004	-32	-52	-6
BA 19/37		3.32	0.042	-22	-54	-12
Right retrosplenial/posterior cingulate region	< 0.001					
BA 23/30		5.28	0.001	20	-54	16
Right posterior middle frontal region	0.043					
BA 6		5.11	0.001	-26	-2	62
Left occipital region	< 0.001					
BA 17/18		4.25	0.007	-6	-94	-4
BA 18		4.05	0.011	-12	-82	-8
BA 18/19		4.47	0.004	-26	-82	-8
OLD vs. YOUNG						
Right superior temporal/perisylvian region	< 0.001					
BA 22		4.05	0.008	60	-8	-4
BA 22/40		4.20	0.007	64	-16	14
"		4.14	0.007	56	-18	14
Left superior temporal/perisylvian region	< 0.001					
BA 22/40		4.88	0.006	-60	-18	14
Inferior posterior insula/temporoparietal operculum		5.31	0.005	-30	12	-18
BA 4/6		4.45	0.006	-58	2	8

Medial superior frontopolar region	< 0.001					
Left BA 10		4.85	0.006	-8	60	12
Right BA 10		4.69	0.006	6	56	4
Right anterior cingulate region						
BA 24/32		4.35	0.006	6	34	0
Left mid-posterior cingulate region	0.024					
BA 23/31		4.39	0.006	-2	-22	38
Precuneus/posterior cingulate region	0.009					
Right BA 7		4.1	0.008	6	-60	38
Left BA 31		3.84	0.01	-4	-62	26
Left BA 23		3.65	0.013	-8	-50	28
Subcortical areas	0.002					
Anterior thalamus		4.09	0.008	-10	-4	18
Medio-dorsal thalamus		3.78	0.011	-20	-18	22
Caudate nucleus		4.03	0.008	-16	-26	20

Note: All P-values are corrected for multiple non-independent comparisons. The coordinates of the local maxima refer to the stereotactic space provided by the MNI (Montreal Neurological Institute) brain [Evans et al., 1993].

Route recognition versus visuo-motor control condition

Similar to route encoding, the occipital-parietal and occipital-temporal areas outlining the dorsal and ventral visual streams were bilaterally activated in the route recognition versus the visuo-motor control condition in both groups of subjects (**figure 1**). The second level comparison young versus old (**figure 2, table 2**) revealed that young subjects showed larger BOLD signal intensity differences between the route recognition condition and the visuo-motor control condition than old subjects in an inferior occipital (BA 17/18/19) and a superior parietal region (BA 7). In contrast, old subjects showed larger BOLD signal intensity differences between the route recognition condition and the visuo-motor control condition than young subjects in the left angular gyrus (BA 39), the left superior temporal region (BA 21, 22 and 38), the anterior and posterior cingulate (BA 32 and 23/31), and the right anterior part of the thalamus as well as medial frontal regions (BA 10, 11, 45 and 47). Again, most of these effects represent smaller reductions relative to the visuo-motor control in the old group. However, the old group activated the right middle-inferior frontal gyrus (BA 45), while the young subject showed deactivations in these regions relative to the baseline provided by the visuo-motor control condition.

Table 2

Significant differences of activity in the contrast route recognition versus visuo-motor control.

Region Brodmann's area	Cluster P-value	Z-score	Voxel P-value	[x y z]		
YOUNG vs. OLD						
Bilateral middle/inferior occipital extending into the lingual/fusiform regions	< 0.001					
Right BA 17		4.68	0.004	18	-94	48
"		5.33	<0.001	12	-82	-2
Left BA 17		4.94	0.001	-6	-92	-2
"		5.02	<0.001	16	-88	-6
Right BA 18		4.82	0.003	36	-82	-6
"		4.79	0.004	12	-90	4
"		4.01	0.006	28	-84	12
Left BA 18		5.28	<0.001	30	-84	-6
"		5.63	<0.001	-10	-86	-8
"		3.70	0.010	-18	-64	14
Right BA 18/19		4.92	0.004	26	-66	6
"		4.98	0.001	20	-84	16
"		4.87	<0.001	16	-80	10
Left BA 18/19		4.50	0.004	-24	-56	-4
"		5.06	<0.001	-20	-74	0
Right BA 19		5.46	<0.001	30	-70	-6
Left BA 19		5.85	<0.001	-28	-82	-6
"		4.08	0.006	-14	-94	20
Right BA 19/37		5.80	<0.001	26	-58	-10
Left BA 19/37		4.49	0.004	-24	-58	-12
Left BA 37		4.97	0.001	-30	-52	-8
Right retrosplenial/posterior cingulate region						
BA 23/30		5.67	<0.001	22	-56	20
Left superior parietal region	0.012					
BA 7		5.30	<0.001	-14	-58	64
"		4.85	0.004	-12	-50	58
OLD vs. YOUNG						
Right anterior temporal/medio-temporal region	< 0.001					
BA 36		4.64	0.004	28	-14	-24
BA 28/34		4.42	0.004	26	-8	-26
BA35/28/hippocampus		4.57	0.004	20	-14	-14
"		4.52	0.004	22	-10	-14
Anterior hippocampus/amygdala		4.44	0.004	28	-2	-12

Anterior hippocampus/amygdala		4.40	0.004	24	-4	-12
BA 22		4.73	0.004	62	0	6
"		4.65	0.004	54	-8	4
BA 22/38		4.79	0.004	58	-2	-8
BA 22/42		3.83	0.008	64	-18	12
Mid-posterior insula		4.26	0.005	44	-4	-8
Perisylvian BA 40		3.55	0.011	54	-26	20
Left anterior medial temporal region	0.001					
Anterior hippocampus/amygdala		4.05	0.006	-30	-2	-18
Hippocampus		3.85	0.007	-24	-10	-14
Left inferior parietal region	0.01					
BA 39/40		4.62	0.004	-56	-64	24
"		3.91	0.007	-58	-64	14
Left anterior superior/middle temporal region	0.001					
BA 21/22		4.57	0.004	-62	-6	-6
BA 22		3.80	0.008	-60	-18	2
BA 38		3.95	0.007	-56	12	-4
Fronto-polar/medial superior frontal/ anterior cingulate region	< 0.001					
BA 10/32		4.32	0.005	0	58	2
BA 11/32		4.21	0.005	0	52	-12
Left BA 10		4.11	0.005	-6	62	12
Left BA 47		3.80	0.008	-30	14	-18
Right middle-inferior frontal region	0.065					
BA 45		4.30	0.005	58	22	10
BA 47		3.58	0.010	50	28	-8
"		3.54	0.011	44	30	-14
Right retrosplenial/posterior cingulate region	0.001					
BA 7/31		4.29	0.005	10	-56	38
BA 31		3.49	0.012	0	-42	36
BA 30/31		3.82	0.008	6	-52	32
Subcortical areas	0.001					
Anterior thalamus		5.00	0.001	0	-2	8
Right caudate nucleus		3.31	0.020	16	-6	14
"		4.16	0.005	10	-6	20
Left globus pallidus		3.21	0.020	-14	6	-4
Right LGN		4.94	0.004	14	-20	-14
Midbrain		3.87	0.007	-4	-6	-8
"		3.83	0.008	-4	0	-6
"		3.88	0.007	2	-16	-20

Note: All P-values are corrected for multiple non-independent comparisons. The coordinates of the local maxima refer to the stereotactic space provided by the MNI (Montreal Neurological Institute) brain (Evans et al., 1993).

Route encoding versus route recognition in young versus old

Table 3 and Figure 3 show the results for the contrast route encoding versus recognition when comparing young with old subjects. As compared to old subjects, young subjects showed larger BOLD signal intensity differences between the route encoding and the route recognition condition in parts of the dorsal and ventral visual streams (left BA 18, 19, 37; right BA 7/40 and 19) as well as the right anterior parahippocampal gyrus. Finally, a small region within the supplementary motor area was relatively more activated (BA 6/8) in young as compared to old subjects.

Exploring further the basis for these interactions just described, we plotted the parameter estimates in local maxima separately for young and old subjects as well as both contrast: route encoding versus visuo-motor control and route recognition versus visuo-motor control (**figure 4**). Older subjects show indeed weaker encoding related activity than young subjects in posterior fusiform/parahippocampal, and supramarginal regions. In contrast, the young subjects exhibit weaker recognition related activity in the anterior parahippocampal region than old subjects. It is important to note that the activity in this region is on a lower level during both memory conditions than the visuo-motor control condition.

Table 3

Significant differences of activity in the contrast route encoding versus route recognition.

Region **Brodmann's area**	**Cluster** **P-value**	**Z-score**	**Voxel** **P-value**	**[x y z]**		
YOUNG vs. OLD						
Right inferior temporal-occipitotemporal region	0.054					
BA 34		4.00	0.016	20	-12	-12
BA 28/36		3.67	0.023	24	-14	-22
Posterior BA 36		4.93	0.006	28	-38	-18
BA 37		4.26	0.012	28	-46	-8
BA 18		4.19	0.013	6	-66	2
***Left inferior temporal*–occipitotemporal region**	< 0.001					
BA 19/37		5.21	0.005	-48	-64	-12
"		4.23	0.012	-42	-56	-16
"		3.85	0.018	-26	-54	-12

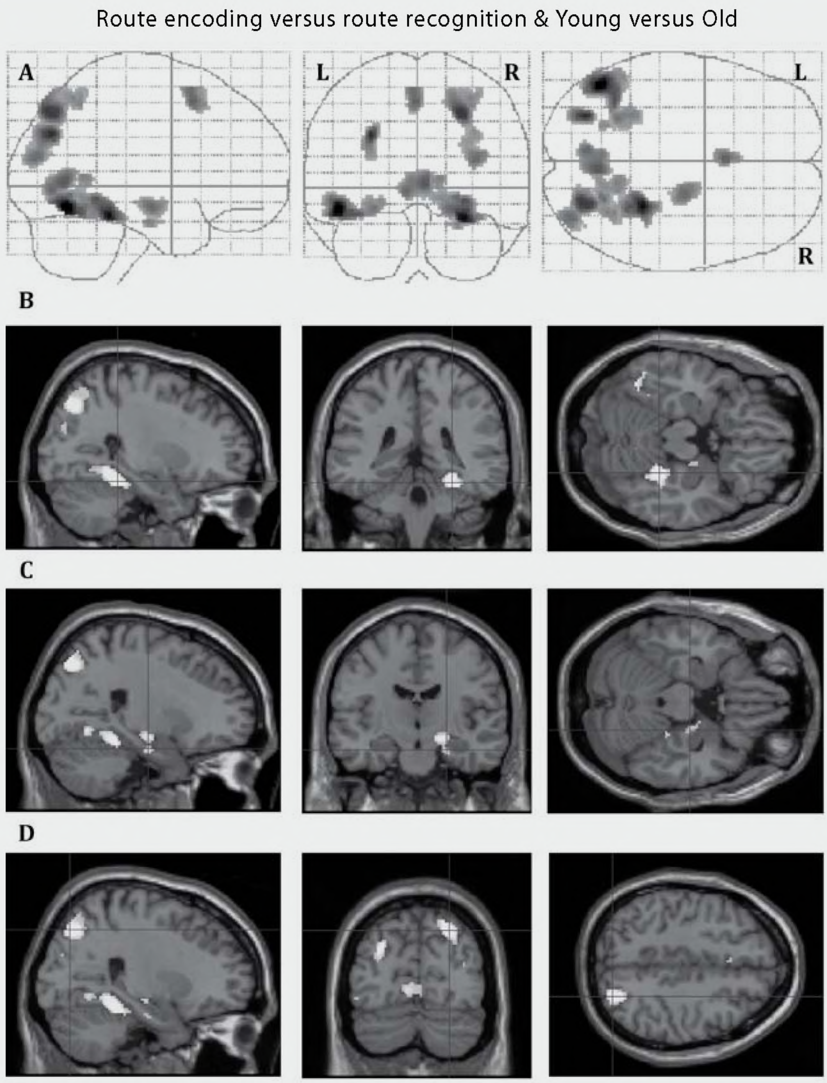
Left inferior parietal-superior occipital region	0.034					
BA 19/39		4.65	0.007	-28	-74	32
Right parietal lobe	< 0.001					
BA 7		4.58	0.008	26	-76	46
BA 7/40		3.65	0.023	32	-56	50
BA 19		3.96	0.017	36	-82	18
Medial superior frontal gyrus	0.095					
BA 6/8		4.11	0.014	-2	12	52
OLD vs. YOUNG						
Perisylvian region	< 0.001					
BA 4/6		3.89	0.062	-44	2	10
BA 22		4.35	0.062	-60	-16	16
BA 40/43		4.34	0.062	-50	-14	22
Anterior cingulate region	< 0.001					
Right BA 24/32		4.07	0.062	6	32	0
Left BA 24/32		4.26	0.062	-10	44	4
Right anterior lentiform - caudate nucleus		3.98	0.062	18	24	-6

Note: All P-values are corrected for multiple non-independent comparisons. The coordinates of the local maxima refer to the stereotactic space provided by the MNI (Montreal Neurological Institute) brain (Evans et al., 1993).

Route encoding versus route recognition in old versus young

The results from the contrast route encoding versus recognition, comparing older versus younger subjects can be seen in table 3 and figure 5. Older subjects showed larger BOLD signal intensity differences between the route encoding and the route recognition condition than young subjects in the left perisylvian region (including BA 4/6, BA 22 and BA 40/43) and the anterior cingulate (bilateral BA 24/32; **figure 5C**). Again, to explore further the basis for these interactions, we plotted the parameter estimates in local maxima separately for young and old subjects as well as both contrast: route encoding versus visuo-motor control and route recognition and visuo-motor control (**figure 6**). Data depicted in Figure 6 show that young subjects suppress, particularly during route encoding, activity in the superior temporal and anterior cingulate gyri more effectively than old subjects. Hence, these relative activations in old subjects seem to be based on smaller activity reductions and not true increases of activity above the baseline provided by the visuo-motor control condition.

Figure 3
Brain regions that show relatively greater activity in young than old subjects during route encoding compared to route recognition. While section A shows a whole brain projection of activations, sections B to D depict local maxima of the most relevant activations in the right fusiform gyrus (B, BA 36/37; [x y z] = [28 -38 -18]), the right anterior parahippocampal gyrus (C, [24 -14 -22]; BA 28/36) and the right superior parietal region (D, BA 7; [26 -76 46]).



2

Figure 4
Parameter estimates of experimental effects (arbitrary units) in local maxima separately plotted for old and young subjects as well as both contrasts: route encoding vs. visuo-motor control and route recognition vs. visuo-motor control.

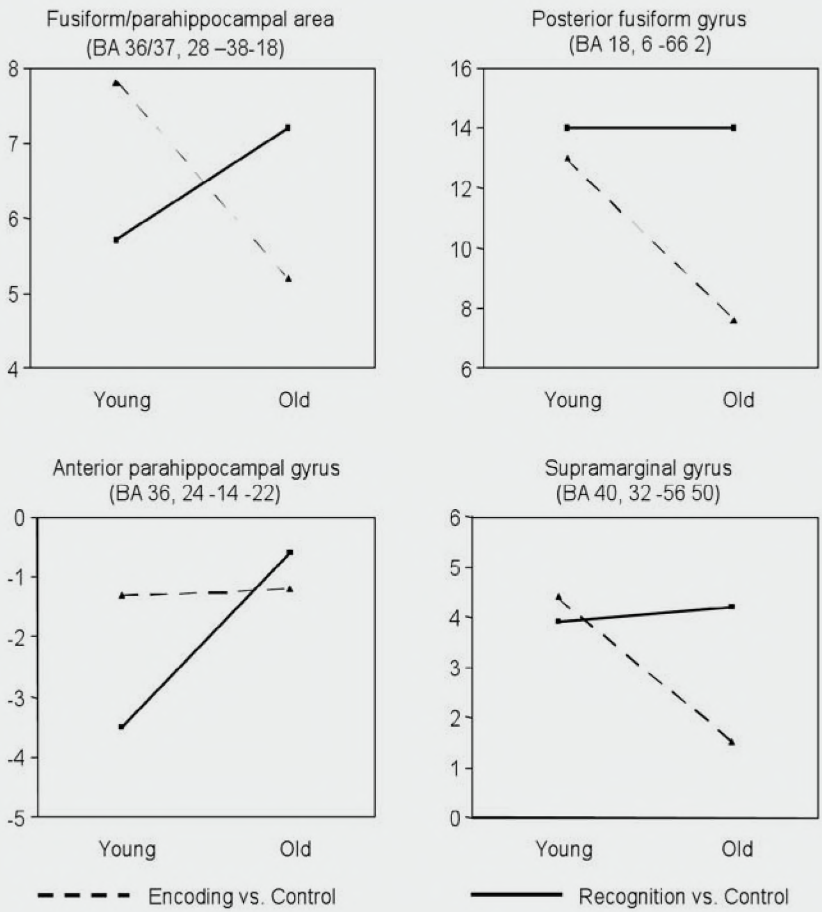


Figure 5
Brain regions that show relatively greater activity in old than young subjects during route encoding compared to route recognition. While section A shows a whole brain projection of activations, sections B and C depict local maxima of most relevant activations in the left perisylvian region (B, BA 22 ; [-60 -16 16]) and the anterior cingulate cortex (C, BA 24/32; [6 32 0]).

Route encoding versus route recognition & Old versus Young

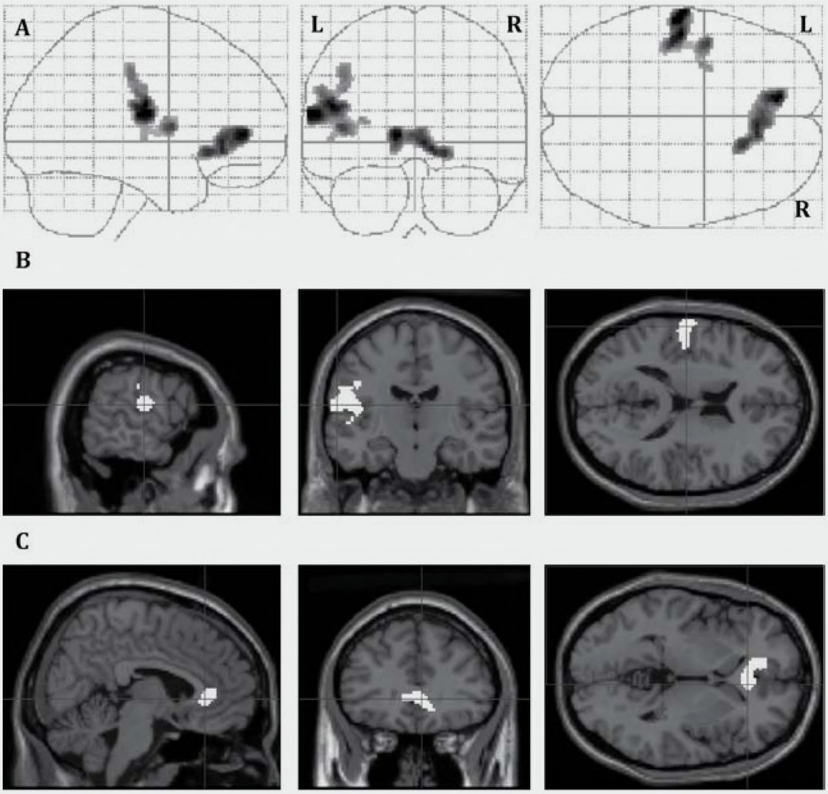
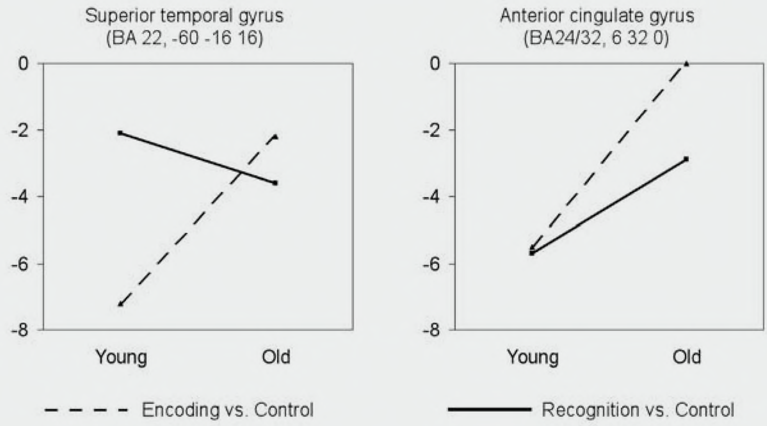


Figure 6
Parameter estimates of experimental effects (arbitrary units) in local maxima separately plotted for old and young subjects as well as both contrasts: route encoding vs. visuo-motor control and route recognition vs. visuo-motor control.



Discussion

The behavioral results indicate that both groups of subjects were able to learn and effectively solve the recognition task. However, there was a small but significant difference in performance between groups. It is likely that this difference is attributable to subtle spatial memory deficits in our sample of older subjects, consistent with previous findings (Kirasic, 1991; Kirasic et al., 1992; Wilkniss et al., 1997; Moffat et al., 2001; Moffat & Resnick 2002; for review see Kirasic, 2001).

Route encoding versus visuo-motor control and route recognition versus visuo-motor control activated a neural network known to be involved in spatial navigation and memory (for review, see Burgess et al., 2002). These activations comprise the dorsal and ventral visual stream (Mishkin et al., 1983; Ungerleider & Haxby, 1994) and include the frontal eye fields (Corbetta et al., 2002). Our behavioral and imaging findings indicate that the task used in the present study is well suited to investigate the neural correlates of navigational memory deficits in old age.

During encoding, old subjects show as compared to young subjects diminished posterior fusiform/parahippocampal and parietal activity (**figure 3** and **4**). It has been suggested that this area supports memory formation of complex visual stimuli with a spatial layout (Brewer et al., 1998; Kirchhoff et al., 2000; Weis et al., 2004) and geometric analysis of the local environment (Epstein and Kanwisher, 1998). Furthermore, single-cell recordings in humans indicate that landmark information is stored in the parahippocampal cortex (Ekstrom et al. 2003), which covers the posterior half of the parahippocampal gyrus and the medial bank of the fusiform gyrus (Amaral and Insausti, 1990). Also the parietal area is known to be critically involved in declarative memory formation for visuo-spatial information (Kirchhoff et al., 2000; Weis et al., 2004). Hence, old subjects seem to exhibit a route encoding deficit based on reduced functionality of posterior fusiform/parahippocampal and parietal areas. This finding is in accordance with prior functional imaging studies investigating the neural correlates of age differences in memory performance using non-spatial stimuli and it underlines the existence of critical age differences in memory formation (e.g. Grady et al., 1995; Daselaar et al., 2003; Morcom et al., 2003; Schiavetto et al., 2002).

The reduced route recognition related activity in the anterior parahippocampal region of young subjects is more difficult to interpret, because this region seems to be less activated during both memory conditions than the visuo-motor control condition. Hence, it is questionable whether this region was contributing to memory performance in the present task. Moreover, there is an ongoing discussion about the precise role of the anterior parahippocampal region in declarative memory (Schacter and Wagner, 1999). At least, it has been shown that this region plays a critical role in the formation of new declarative memories with an activity increase (Fernandez et al., 1999, 2002; Grasby et al., 1993; Otten et al., 2001; Petersson et al., 1999a; Strange et al., 2002; Tulving et al., 1999; Weis et al., 2004) and in recognition based on familiarity with an activity decrease (Brown and Aggleton, 2001; Henson et al., 2003). Thus, one might speculate that the reduced recognition related activity in the anterior parahippocampal gyrus in young subjects (**figure 4**) is a correlate of a familiarity signal during route recognition, which is weaker or even not existing in old subjects. This speculation seems to contradict the often-replicated behavioral finding that older adults show generally no deficit in familiarity-based recognition (e.g., Rabinowitz, 1984; Parkin and Walter, 1992; Mantyla, 1993; Clarys et al., 2002). However, healthy old adults with reduced medial temporal lobe functionality show also a reduced recognition performance, when recognition judgments were based on a feeling of familiarity (Davidson and

Glisky, 2002). Thus, the missing anterior parahippocampal activity decrease during route recognition in old subjects might indeed indicate an abolished familiarity signal.

Another age difference in brain activation found during route encoding is the diminished perisylvian deactivation in old subjects (**figure 5B** and **6**). This effect might be related to a deficit in suppressing irrelevant input like scanner noise in old age. Several studies investigating the neural correlates of attentional modulation of visual processing tasks found that task irrelevant processing needs to be suppressed, by deactivation of, for instance, the auditory cortex (Ghatan et al., 1998; Petersson et al., 1999b; Shulman et al., 1997; Gisselgård et al., 2003). Also the relatively stronger activation of the anterior cingulate cortex in old subjects as compared to young (**figure 5C** and **6**) can be explained by a failure to suppress or inhibit irrelevant, particularly internal information (Gusnard et al., 2001). Young subjects seemed to be able to suppress activity in these regions during both memory conditions, but old subjects seem to be less effective in doing so, particularly during route encoding. Thus, old subjects might have a relative difficulty in focusing their attention to the relevant input and disregarding the irrelevant aspects of the sensory input or internal information. In other words, the old group may not be able to optimize there processing resources for the task at hand.

In conclusion, the old subjects in the present study showed a subtle navigational memory deficit. Causes of this impairment appear to be related to deficits in spatial memory formation and less effective attentional mechanisms during route encoding. It seems that elderly subjects encode navigational information less effective than young subjects, likely associated with reduced involvement of the dorsal and ventral visual streams extending into the posterior fusiform/parahippocampal area. In addition, older subjects may be less effective during route encoding in suppressing irrelevant information by attentional mechanisms as indicated by less suppressed activity in perisylvian and anterior cingulate cortices. In contrast, age differences in neural correlates of route recognition seem to be rather subtle. We found in old subjects an indication for an anterior parahippocampal dysfunction, which might be explained by a diminished familiarity signal during route recognition.

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References

Adler, R. J., 1981. The Geometry of Random Fields. Wiley and Sons, New York.

Aguirre, G.K., D'Esposito, M., 1997. Environmental knowledge is subserved by separable dorsal/ventral neural areas. J Neurosci 17, 2512-8.

Aguirre, G.K., Detre, J.A., Alsop, D.C., D'Esposito, M., 1996. The parahippocampus subserves topographical learning in man. Cereb Cortex 6, 823-9.

Amaral, D.G., Insausti, R.. 1990. Hippocampal formation. In: Paxinos, G. (Ed.), The Human Nervous System. San Diego: Academic Press, pp. 711-755.

Brewer, J.B., Zhao, Z., Desmond, J.E., Glover, G.H., Gabrieli, J.D., 1998. Making memories: brain activity that predicts how well visual experience will be remembered. Science 281, 1185-7.

Brown, M.W., Aggleton, J.P., 2001. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat Rev Neurosci 2, 51-61.

Burgess, N., Maguire, E.A., O'Keefe, J., 2002. The human hippocampus and spatial and episodic memory. Neuron 35, 625-41.

Burns, P.C., 1999. Navigation and the mobility of older drivers. J Gerontol B Psychol Sci Soc Sci 54, S49-55.

Cabeza, R., 2002. Hemispheric Asymmetry Reduction in Older Adults: The HAROLD Model. Psychol Aging 17, 85-100.

Cabeza, R., McIntosh, A.R., Tulving, E., Nyberg, L., Grady, C.L., 1997. Age-related differences in effective neural connectivity during encoding and recall. Neuroreport 8,3479-83.

Cabeza, R., Anderson, N.D., Locantore, J.K., McIntosh, A.R., 2002. Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults. NeuroImage 17, 1394-1402.

Clarys, D., Isingrini, M., Gana, K., 2002. Mediators of age-related differences in recollective experience in recognition memory. Acta Psychol 109, 315-29

Corbetta, M., Kincade, J.M., Shulman, G.L., 2002. Neural systems for visual orienting and their relationships to spatial working memory. J Cogn Neurosci 14, 508-23.

Daselaar, S.M., Veltman, D.J., Rombouts, S.A.R.B., Raaijmakers, J.G.W., Jonker, C., 2003. Neuroanatomical correlates of episodic encoding and retrieval in young and elderly subjects. Brain 126, 43-56.

Davidson, P.S., Glisky, E.L., 2002. Neuropsychological correlates of recollection and familiarity in normal aging. Cogn Affect Behav Neurosci 2, 174-86.

Dolcos, F., Rice, H.J., Cabeza, R., 2002. Hemispheric asymmetry and aging: right hemisphere decline or asymmetry reduction. Neurosci Biobehav Rev 26, 819-825.

Ekstrom, A.D., Kahana, M.J., Caplan, J.B., Fields, T.A., Isham, E.A., Newman, E.L., Fried, I., 2003. Cellular networks underlying human spatial navigation. Nature 425, 184-188.

Epstein, R., Kanwisher, N., 1998. A cortical representation of the local visual environment. Nature 392, 598-601.

Evans, A.C., Collins, D.L., Mills, S.R., Brown, E.D., Kelly, R.L., Peters, T.M., 1993. 3D statistical neuroanatomical models from 305 MRI volumes. Proc IEEE-Nuclear Science Symposium and Medical Imaging Conference, 1813-1817.

Fernández, G., Effern, A., Grunwald, T., Pezer, N., Lehnertz, K., Dümpelmann, M., et al, 1999. Real-time tracking of memory formation in the human rhinal cortex and hippocampus. Science 285, 1582-5.

Fernández, G., Klaver, P., Fell, J., Grunwald, T., Elger, C.E., 2002. Human declarative memory formation: segregating rhinal and hippocampal contributions. Hippocampus 12, 514-9.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-B., Frackowiak, R.S.J., 1995. Statistical parametric maps in functional imaging: A general linear approach. Hum Brain Mapp 2, 189-210.

Genovese, C.L., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. NeuroImage 15, 870-878.

Ghatan, P.H., Hsieh, J.C., Petersson, K.M., Stone-Elander, S., Ingvar, M., 1998. Coexistence of attention-based facilitation and inhibition in the human cortex. NeuroImage 7, 23-9.

Gisselgård, J., Petersson, K.M., Baddeley, A., Ingvar, M, 2003. The Irrelevant Speech Effect: A Pet Study. Neuropsychologia 41: 1899-1911.

Grady, C.L., Craik, F.I., 2000. Changes in memory processing with age. Curr Opin Neurobiol 10, 224-31.

Grady, C.L., McIntosh, A.R., Horwitz, B., Maisog, J.M., Ungerleider, L.G., Mentis, M.J., Pietrini, P., Schapiro, M.B., Haxby, J.V., 1995. Age-related reductions in human recognition memory due to impaired encoding. Science 269, 218-221.

Grady, C.L., McIntosh, A.R., Craik, F.I., 2003. Age-Related Differences in the Functional Connectivity of the Hippocampus During Memory Encoding. Hippocampus 13, 572-586.

Grasby, P.M., Frith, C.D., Friston, K., Frackowiak, R.S., Dolan, R.J., 1993. Activation of the human hippocampal formation during auditory-verbal long-term memory function. Neurosci Lett 163, 185-8.

Gusnard, D.A., Akbudak, E., Shulman, G.L., Raichle, M.E., 2001. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. Proc Natl Acad Sci U S A 98,4259-64.

Henson, R.N., Cansino, S., Herron, J.E., Robb, W.G., Rugg, M.D., 2003. A familiarity signal in human anterior medial temporal cortex? Hippocampus 13, 301-4.

Kirasic, K.C., 1991. Spatial cognition and behavior in young and elderly adults: implications for learning new environments. Psychol Aging 6, 10-8.

Kirasic, K.C., 2001. Aging and spatial behavior in the elderly adult. In: Kitchin R, Freundschun S. (Eds.), Cognitive Mapping: Past, present, and future. Routledge Frontiers of Cognitive Science, Taylor and Francis, pp. 166-178.

Kirasic, K.C., Allen, G.L., Haggerty, D., 1992. Age-related differences in adults' macrospatial cognitive processes. Exp Aging Res 18, 33-39.

Kirchhoff, B.A., Wagner, A.D., Maril, A., Stern, C.E., 2000. Prefrontal - Temporal Circuitry for Episodic Encoding and Subsequent Memory. J Neurosci 20, 6173-6180.

Logan, J.M., Sanders, A.L., Snyder, A.Z., Morris, J.C., Buckner, R.L., 2002. Under-recruitment and nonselective recruitment: dissociable neural mechanisms associated with aging. Neuron 33, 827-40.

Maguire, E.A., Burgess, N., Donnett, J.G., Frackowiak, R.S., Frith, C.D., O'Keefe, J., 1998a. Knowing where and getting there: a human navigation network. Science 280, 921-4.

Maguire, E.A., Frith, C.D., Burgess, N., Donnett, J.G., O'Keefe, J., 1998b. Knowing where things are parahippocampal involvement in encoding object locations in virtual large-scale space. J Cog Neurosci 10, 61-76.

Mantyla, T., 1993 Knowing but not remembering: adult age differences in recollective experience. Mem Cognit 21, 379-88.

Mishkin, M., Ungerleider, L.G., Macko, K.A., 1983. Object vision and spatial vision: two cortical pathways. Trends Neurosci 6, 414-417.

Moffat, S.D., Zonderman, A.B., Resnick, S.M., 2001. Age differences in spatial memory in a virtual environment navigation task. Neurobiol Aging 22, 787-796.

Moffat, S.D., Resnick, S.M., 2002. Effects of age on virtual environment place navigation and allocentric cognitive mapping. Behav Neurosci 116, 851-859.

Morcom, A.M., Good, C.D., Frackowiak, R.S.J., Rugg, M.D., 2003. Age effects on the neural correlates of successful memory encoding. Brain 126, 213-229.

Morris, J.C., 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 43, 2412-2414.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97-113.

Otten, L.J., Henson, R.N., Rugg, M.D., 2001. Depth of processing effects on neural correlates of memory encoding: relationship between findings from across- and within-task comparisons. Brain 124, 399-412.

Parkin, A.J., Walter, B.M., 1992. Recollective experience, normal aging, and frontal dysfunction. Psychol Aging 7, 290-8.

Petersson, K. M., Reis, A., Castro-Caldas, A., Ingvar, M, 1999a. Effective auditory-verbal encoding activates the left prefrontal and medial temporal lobes: A generalization to illiterate subjects. NeuroImage 10, 45-54.

Petersson, K.M., Elfgren, C., Ingvar, M., 1999b. Dynamic changes in the functional anatomy of the human brain during recall of abstract designs related to practice. Neuropsychologia 37, 567-87.

Rabinowitz, J.C., 1984. Aging and recognition failure. J Gerontol 39, 65-71

Schacter, D.L., Wagner, A.D., 1999. Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. Hippocampus 9, 7-24.

Schiavetto, A., Köhler, S., Grady, C.L., Winocur, G., Moscovitch, M., 2002. Neural correlates of memory for object identity and object location: effects of aging. Neuropsychologia 40, 1428-1442.

Shulman, G.L., Corbetta, M., Buckner, R.L., Raichle, M.E., Fiez, J.A., Miezin, F.M. et al, 1997. Top-down modulation of early sensory cortex. Cereb Cortex 7, 193-206.

Strange, B.A., Otten, L.J., Josephs, O., Rugg, M.D., Dolan, R.J., 2002. Dissociable human perirhinal, hippocampal, and parahippocampal roles during verbal encoding. J Neurosci 22, 523-8.

Talairach, J., Tournoux, P., 1988. Co-Planar Stereotaxic Atlas of the Human Brain. Georg Thieme Verlag, Stuttgart.

Tulving, E., Habib, R., Nyberg, L., Lepage, M., McIntosh, A.R., 1999. Positron emission tomography correlations in and beyond medial temporal lobes. Hippocampus 9, 71-82.

Ungerleider, L.G., Haxby, J.V., 1994. 'What' and 'where' in the human brain. Curr Opin Neurobiol 4, 157-65.

Weis, S., Klaver, P., Reul, J., Elger, C.E., Fernández, G. 2004. Temporal and cerebellar brain regions that support both declarative memory formation and retrieval. Cereb Cortex 14, 256-267.

Wilkniss, S.M., Jones, M.G., Korol, D.L., Gold, P.E., Manning, C.A., 1997. Age-related differences in an ecologically based study of route learning. Psychol Aging 12, 372-375.

Worsley, K.J., Friston, K.J., 1995. Analysis of fMRI time-series revisited - again. NeuroImage 2, 173-181.

Worsley, K.J., Marrett, S., Neelin, P., Vandal, A.C., Friston, K.J., Evans, A.C., 1996. A unified statistical approach for determining significant signals in images of cerebral activation. Hum Brain Mapp 4, 58-73.

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Chapter

Age-effects on associative object-location memory

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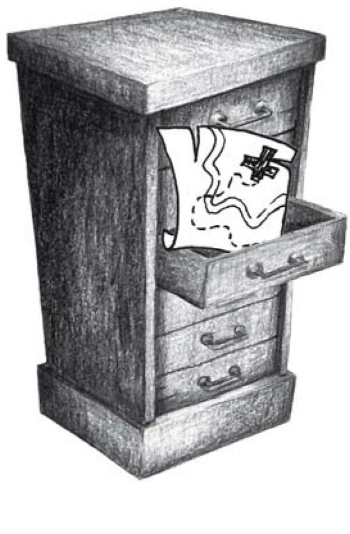


Abstract

Aging is accompanied by an impairment of associative memory. The medial temporal lobe and fronto-striatal network, both involved in associative memory, are known to decline functionally and structurally with age, leading to the so-called associative binding deficit and the resource deficit. Because the MTL and fronto-striatal network interact, they might also be able to support each other. We therefore employed an episodic memory task probing memory for sequences of object-location associations, where the demand on self-initiated processing was manipulated during encoding: either all the objects were visible simultaneously (rich environmental support) or every object became visible transiently (poor environmental support). Following the concept of resource deficit, we hypothesized elderly probably have difficulty using their declarative memory system when demands on self-initiated processing are high (poor environmental support). Our behavioural study showed that only the young use the rich environmental support in a systematic way, by placing the objects next to each other. With the task adapted for fMRI, we found that elderly showed stronger activity than young subjects during retrieval of environmentally-richly encoded information in the basal ganglia, thalamus, left middle temporal/ fusiform gyrus and right medial temporal lobe (MTL). These results indicate that rich environmental support leads to recruitment of the declarative memory system in addition to the fronto-striatal network in elderly, while the young use more posterior brain regions likely related to imagery. We propose that elderly try to solve the task by additional recruitment of stimulus-response associations, which might partly compensate their limited attentional resources.

Introduction

One of the most common memory complaints of elderly is that they are unable to remember the location of household objects, like keys (e.g. Jonker, et al. 1996).

These complaints are part of an age-related episodic memory decline (for review, see Hedden and Gabrieli 2004), in particular of contextual memory. For instance, elderly show problems remembering which of two experimenters presented a target (McIntyre and Craik 1987, Schacter, et al. 1994), what gender the presenter was (e.g. Simons, et al. 2004), or what the target's case format was (e.g. Kausler and Puckett 1981) and what colour the target was presented in at study (Park and Puglisi 1985, see Spencer and Raz 1995 for a review). Given that item memory stays generally intact (Craik and McDowd 1987) (for a recent meta-analysis, see Old and Naveh-Benjamin 2008), it was hypothesised that elderly are impaired at binding contextual elements into a coherent episode, also called the associative deficit (Naveh-Benjamin 2000). Adding to the age-related associative deficit is the so-called resource deficit (Craik and Byrd 1982), which posits that a lack of cognitive, in particular attentional resources makes it difficult to use self-initiated processes.

With age, several brain structures essential for self-initiated processes (the fronto-striatal network) and associative memory (the Medial Temporal Lobe; MTL) deteriorate structurally with age. Foremost, lateral prefrontal cortex volume decreases around 5% per decade, starting at age 20 (Raz, et al. 2005, Resnick, et al. 2003). Decline in the basal ganglia is also apparent, for instance, caudate volume declines with 0,75% per year (Raz, et al. 2005). Similar decline is observed in the hippocampus (0.79%), but age-related degeneration of the frontal lobe is the most prominent.

Next to structural decline, also age-related functional decline is observed. For instance, the hippocampus, which is well known to be involved in encoding and retrieval of between-domain associations (Mayes, et al. 2007), often shows decreased activation in elderly during encoding (e.g. Mitchell, et al. 2000) and retrieval (e.g. Cabeza, et al. 2004). Furthermore, elderly show reduced performance on several memory tasks, like cued recall (e.g. Craik and McDowd 1987), source memory (e.g. Wegesin, et al. 2000) and associative memory (Chalfonte and Johnson 1996, Glisky, et al. 2001, Naveh-Benjamin 2000, 2004, 2003). Implicitly imposing strategic processing during encoding enhances source memory performance (Wegesin, et al. 2000). However, explicitly imposing strategic processing during encoding and retrieval does not entirely eliminate the associative deficit (Naveh-Benjamin, et al. 2007). This indicates elderly probably not only have problems with self-initiation (like implementing strategies), they might also be unable to optimally use the strategies that are offered to them (Dunlosky and Hertzog 1998).

The MTL and fronto-striatal network are known to interact with each other (e.g. Poldrack and Packard 2003, Poldrack and Rodriguez 2004). This has been observed in stimulus-response learning (Poldrack, et al. 1999), but also in object-location associative memory (Iaria, et al. 2003). Since the MTL and fronto-striatal network interact, they might also be able to compensate for each other. This was for instance observed in patients with specific damage to the caudate nucleus by Voermans and colleagues (2004). They showed that activation of the right hippocampus compensated for gradual functional degradation of the caudate nucleus in a route recognition task. In healthy young adults, an increased interaction was found between the caudate and hippocampus. This indicates that the hippocampus can compensate for reduced caudate processing when necessary.

Here we aim to investigate if elderly show compensatory activity in the fronto-striatal network in an object-location associative memory retrieval task, where the demand on self-initiated processing is manipulated during encoding only. Following the concept of resource deficit, elderly probably have difficulty using their declarative memory system when demands on self-initiated processing are high, which can be established by offering little contextual information (or so-called environmental support (Craik, et al. 1987). The task used is the same as used by De Rover et al. (2008). They investigated self-initiated processes in an fMRI study using an episodic memory task for sequences of object-location associations in a grid. Here, the structure of the sequence during encoding could implicitly influence the representation used at retrieval. During encoding, either all the objects were visible simultaneously (rich environmental support) or every object became visible transiently (poor environmental support). They found that young adults adapted their representation used at retrieval to the encoding cues available. Rich environmental support during encoding rendered activation in regions related to mental imagery (Wheeler, et al. 2000), such as the fusiform gyrus, the lingual gyrus and cuneus during retrieval, in addition to areas generally found active during retrieval tasks. In turn, poor environmental support during encoding rendered activation in the globus pallidus and thalamus during retrieval; structures that are generally involved in memory where temporal information is crucial (Ivry and Spencer 2004, Packard and Knowlton 2002, Vakil, et al. 2000).

We hypothesise that elderly will not be able to use the environmental support as systematically as the young use it (imagery), due to a lack of attentional resources. To investigate if the elderly use the extra environmental support in the same systematic way as the young, we first conducted a complementary behavioural experiment with unconstrained response order during recall in young and elderly adults, in which the encoding conditions were identical to the ones used in the fMRI experiment, to make sure any differences between conditions during retrieval are exclusively attributable to differences occurring at encoding.

Participants had to encode sets of 9 object-location associations in a 3 x 3 grid while either a rich environmental encoding structure was provided (all objects visible simultaneously), or while a poor environmental encoding structure was provided (isolated objects becoming visible sequentially). At recall, participants were instructed to reconstruct the grid freely.

To investigate the neural basis of this hypothesised absence of visual imagery in elderly and the putative fronto-striatal support to the declarative memory system, we applied the same task as described above in an fMRI study with young and elderly participants. Besides large overlap in brain activation between young and elderly participants and conditions (since we investigate only highly educated elderly and there were no perceptual differences during cued-recall), we expected any specific differences to pertain to the support of the putatively impaired declarative memory system in the elderly, namely, more activation in the fronto-striatal network as a function of age.

This study is especially important for people working with elderly, like geriatricians, psychologists and occupational therapists, as the outcomes might be useful being taken into account when designing training and therapy.

Experimental procedure

Behavioural Experiment

Participants

Twenty-four healthy volunteers participated in the first experiment (12 young adults (De Rover, et al. 2008), 6 female; mean age = 27.6 years, SD = 3.6, range 21 – 33; 12 elderly participants, 6 female; mean age = 61.8 years, SD = 3.6, range 59 – 70). There was no difference in educational level between the young and the elderly (mean number of years of formal education for the young was 17.6, SD = 0.5; and 17.3, SD = 0.5 for the elderly; $t_{22} = 1.69$, ns.). All but one young and one elderly participant were right-handed as indexed by an Edinburgh handedness index (see also: Oldfield 1971). All elderly participants were high functioning, autonomous community dwellers mostly having an academic degree. The elderly participants, while mostly retired, were all active in cultural pursuits, continuing education or with responsibilities in various associations. None of the healthy elderly had a history of neurological/ psychiatric disease or used psychopharmacological drugs and none reported subjective memory problems. Vision was normal or corrected-to-normal in every participant. All participants gave written informed consent according to the Helsinki Declaration and the local medical ethics committee.

Stimulus material and experimental procedure

We selected 117 black-on-white line drawings of common living and non-living objects (Snodgrass and Vanderwart 1980). We randomly chose 9 drawings (5 living & 4 non-living) for the distraction task, 54 drawings (27 living & 27 non-living) for the environmentally-rich encoding condition and 54 drawings (27 living & 27 non-living) for the environmentally-poor encoding condition. In line with the subsequent fMRI experiment, the behavioural experiment was structured in 12 cycles each including four phases: encoding, distraction, recall test, and visual fixation (**figure 1**). Each cycle started with either a environmentally-rich or a environmentally-poor encoding condition, in which object-location associations were memorized intentionally, and ended with an object-location cued-recall memory test. During encoding, participants were required to memorize nine objects and their particular location in a 3 x 3 grid displayed on a computer screen. The participants were instructed to make a living/ non-living decision on each object and to respond verbally in order to ensure active participation and good recall performance. In the environmentally-rich encoding condition, a red frame moved through the grid in a fixed pseudorandom order highlighting each item for 3 seconds, one item at a time, on which the living/non-living decision was made (**figure 1A**). The complete grid-display with all nine objects was visible during the entire encoding phase providing an environmentally-rich encoding context, in which each item location could easily be associated with neighbouring objects and the entire grid. The environmentally-poor encoding condition was identical to the environmentally-rich study condition except that each object was only transiently visible for 3 seconds, highlighted by the red frame while all other items were hidden by non-informative masks (**figure 1B**). Thus, this condition did not provide simultaneously the entire grid with all objects as an associatively rich spatial structure and its structure was therefore relatively environmentally poor.

To overwrite potentially maintained working memory of the previous encoding phase, we introduced a one-back object memory distraction task (**figure 1C**, Baddely 1995). Participants were shown a 3 x 3 grid with nine novel objects. In this distraction condition, the sequential, random movement of a blue frame over each grid-box was accompanied by a random rearrangement of objects within the grid every 3 seconds. For each object highlighted by the blue frame, participants had to indicate whether this object was identical to the one shown previously in the blue frame independently of the location within the grid over nine successive trials. To parallelise this experiment as much as possible with the subsequent fMRI experiment, we included a visual fixation phase that was equally timed to the other phases (such that every phase lasted 27 seconds). During this condition a white, central fixation cross on a black background was displayed. Participants were instructed to attentively fixate the cross.

During the recall phase, which was identical for the environmentally-rich and the environmentally-poor encoding cycles, participants were presented with a 3 x 3 grid on cardboard, without drawings, as well as the studied objects each printed on a small paper card and provided at once in random spatial positions outside the grid (**figure 1D**). Participants were instructed to put the cards on the 3 x 3 grid on the positions studied during the encoding phase in any order.

Before the actual experiment, participants practiced the task with two cycles (one environmentally-rich and one environmentally-poor study condition) with additional line drawings, which were not otherwise used during the experiment. Participants were comfortably seated at a desk with a computer monitor for stimulus presentation and the 3 x 3 grid in front of them. We used a video camera to record the responses made by the participants for further analysis.

Data analysis

First, the recall performance was analysed per individual, by dividing the number of correct answers by the total number of answers. Next, to investigate if participants used the environmental cues during recall, we analysed the correct answers only.

Specifically, we analysed the relationship between the spatial structure of the grid and the recall order chosen by the participants, in order to determine whether participants used the spatial structure of the grid during retrieval in either of the two conditions (see De Rover, et al. 2008, for details of the analysis). In short, the number of successive correct answers in contiguous positions in the grid (**figure 1**: for instance B1 followed by B2 or A1 would be a contiguous answer, but B1 followed by C3 is a non-contiguous answer) was counted per subject and cycle. This number was expressed as a percentage of the chance level, which was calculated as the number of contiguous correct answers divided by the total number of correct answers available in the grid (taking into account that response options decrease with every placement of an object) and set at 100%.

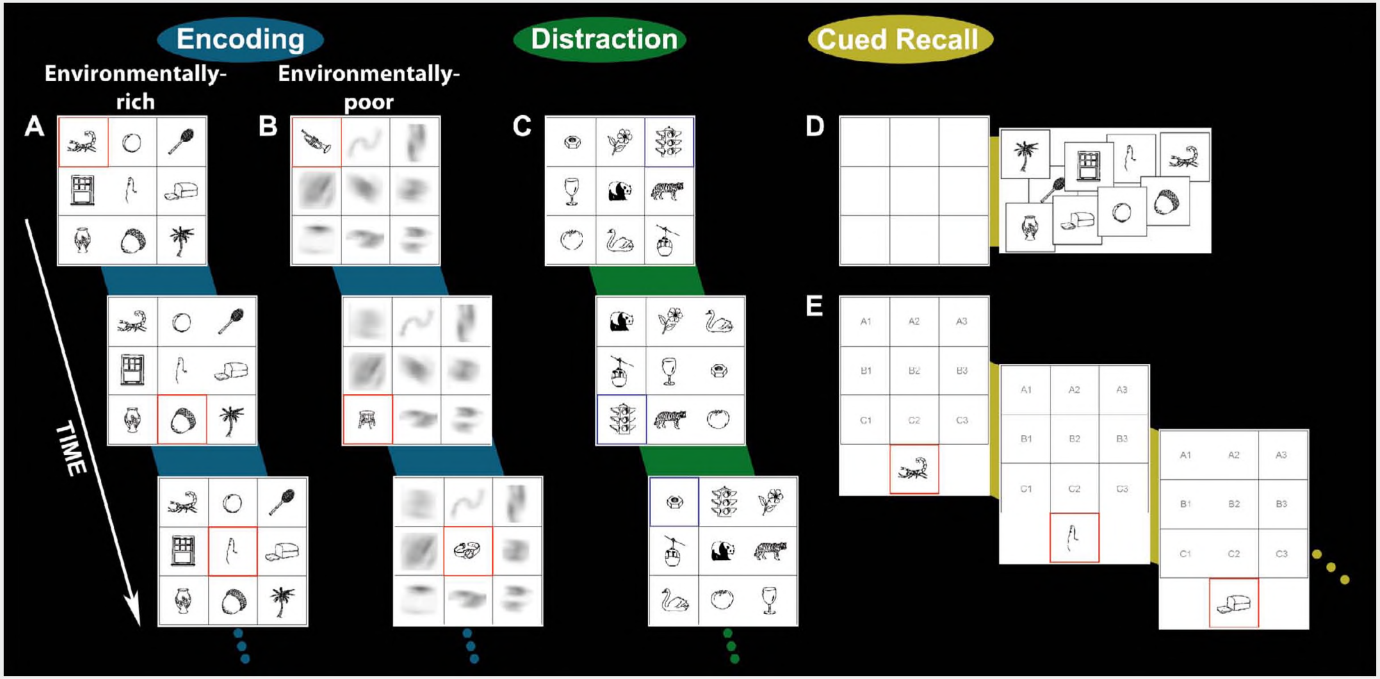
For example, consider a cycle containing only two successive correct answers (B1 followed by A1). The chance that the next correct answer after B1 is in a contiguous position is 0.375, because there are three available contiguous answers following B1: A1, B2 and C1, divided by eight available answers (all 9 positions except B1). The chance level of contiguous correct answers would then be set at 100%, so in this example 0.375 contiguous correct answers are expected by chance. Since the actual number of contiguous correct answers in this example cycle is 1, the percentage of contiguous correct answers is 1 / 0.375 * 100% = 267% of chance level (= 0.375 = 100%) for this particular example cycle.

fMRI Experiment

Participants

Forty healthy volunteers participated in the second experiment (not included in the behavioural experiment; 20 young participants (De Rover, et al. 2008), 10 female; mean age = 25 years, SD = 4, range 19 – 33; 20 elderly participants, 10 female; mean age = 65 years, SD = 4.6, range 60 – 74). There was no difference in education level between the two age groups (mean duration of formal education young 18 years (SD = 2) and elderly 17 years (SD = 0.6), $t_{38} = 1.55$, ns.). All participants were right handed as indexed by an Edinburgh handedness index (Oldfield 1971). All remaining subject characteristics were identical to the ones described for the

Figure 1
Experimental design, demonstrating the timeline of a single cycle. During Environmentally-rich (A) or Environmentally-poor encoding (B), participants made a living/nonliving judgment about the object in the red frame. (A) During Environmentally-rich encoding, all objects were visible simultaneously and continuously. (B) During Environmentally-poor encoding, objects were visible one at a time, while others were covered by a non-informative mask. (C) After encoding, participants were distracted with a one-back object memory task. (D&E) Cued recall, followed by a rest period (fixation cross, not shown). (D) In the behavioural experiment, cued recall comprised a paper version of the grid and objects, so participants could freely reconstruct the grid. (E) In the fMRI experiment, objects were presented sequentially below the grid during cued recall and participants indicated the positions by button presses corresponding to the coordinates in the grid. After cued recall, a rest period involving visual fixation was followed by a new encoding phase (randomly A or B)



behavioural experiment, except for the fact that 4 elderly were on anti-hypertensive medication. The structural MRI investigations did not show any evidence for anatomical abnormalities atypical for age.

Stimulus material and experimental procedure

The fMRI experiment was identical to the behavioural experiment except for: (1) To obtain sufficient power; the second experiment consisted of 20 instead of 12 cycles (**figure 1**). The 20 cycles were separated into two runs of 10 predefined cycles each, which were counterbalanced across participants. Every phase (encoding, distraction, cued recall or rest) lasted 29.7 seconds (9 items 3.3 s each). We selected 189 black-on-white line drawings (9 drawings [5 living and 4 nonliving] for the distraction task, 90 drawings [45 living and 45 non-living] for the environmentally-rich encoding condition and 90 drawings [45 living and 45 non-living] for the environmentally-poor encoding condition); (2) Responses during encoding, distraction and recall were made by appropriate button presses; (3) During the recall task, participants were presented with the 3 x 3 grid without drawings. The participants could read the coordinates of each grid box, A1, A2, … , C3 in the corresponding box. The encoded objects were shown one at a time below the grid in random order (**figure 1E**; 3.3 s per item). Participants were instructed to indicate the coordinate in which the object was presented during the study phase by an appropriate combination of left and right hand button presses.

Before going into the scanner, participants were first thoroughly trained at indicating the different locations in the grid with button presses, to avoid any age-related differences correlated to motor function. Next, they practiced the task in four cycles (two environmentally-rich and two environmentally-poor study conditions) with additional line drawings, which were not otherwise used during the experiment.

We used the Presentation software (www.neurobs.com) to present the stimuli and recorded the responses made by the participants. Stimuli were back-projected via an LCD-projector onto a translucent screen that participants viewed through a mirror mounted on the head coil. Participants responded with two optical key devices, one in each hand. The subject's head was immobilized in order to reduce head motion during fMRI data acquisition. The behavioural responses participants made while in the scanner were analysed for accuracy. The use of different retrieval structures during recall was analysed in the behavioural experiment and thus not further analysed in the fMRI experiment. This approach was chosen, because it allowed us to predefine the response order during recall in the scanner, so that differences in brain activity would not be confounded by any differences in responses.

Data acquisition

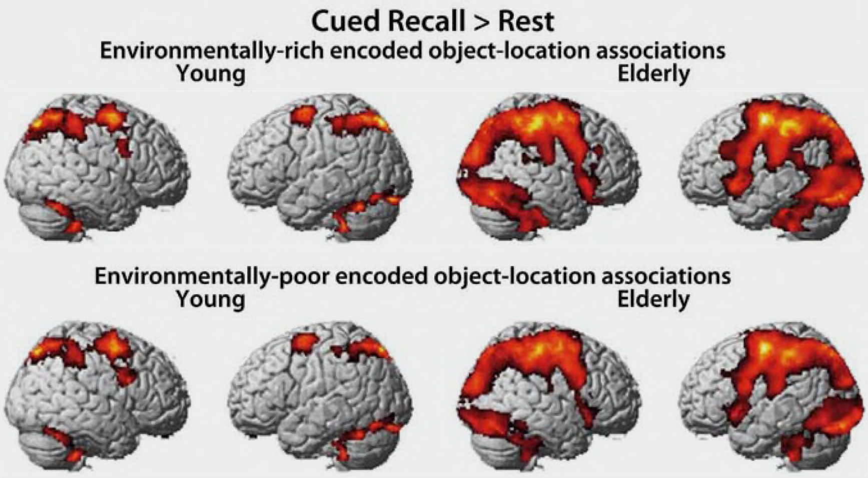
Whole head T2*-weighted EPI-BOLD fMRI data were acquired with a Siemens Sonata 1.5T MR scanner using an interleaved slice acquisition sequence (volume TR = 2.93 s, TE = 40 ms, 90 degree flip-angle, 37 axial slices, slice-matrix size = 64 x 64, slice thickness = 3.5 mm, no slice gap, FOV = 224 mm, isotropic voxel-size = 3.5 x 3.5 x 3.5 mm^3). High-resolution structural MR images were acquired with a T1-weighted MP-RAGE sequence (volume TR = 2.25 s, TE = 3.93 ms, 15 degree flip-angle, 176 sagittal slices, slice-matrix size = 256 x 256, slice thickness = 1 mm, voxel-size = 1x1x1 mm^3).

MR Image preprocessing and statistical analysis

Image preprocessing and statistical analysis was done with the SPM5 software (www.fil.ion.ucl.ac.uk). Functional EPI-BOLD images were realigned and the subject-mean functional MR images were co-registered with the corresponding structural MR images using mutual information optimization. These were subsequently spatially normalized (i.e., the normalization transformations were generated from the structural MR images and applied to the functional MR images) and transformed into standardized MNI space defined by the SPM5 MNI T1 template, and finally the functional images were convolved with an isotropic 3D spatial Gaussian filter kernel of 8 mm (Hayasaka and Nichols 2003, Petersson, et al. 1999). The fMRI data were proportionally scaled to account for global effects and analysed statistically using the general linear model and statistical parametric mapping (Friston, et al. 1994). The linear model included convolved explanatory variables (box-car regressors of the recall phase) modelling the experimental conditions in a blocked fMRI design. The explanatory variables were temporally convolved with the canonical hemodynamic response function provided by SPM5. The realignment parameters were added to the model as regressors of no-interest. Furthermore, to correct for performance differences between cycles within a subject, performance for each cued recall phase was included in the model by parametric modulation of the modelled recall phases. A temporal high pass filter of 128 s was applied to account for various low-frequency effects.

To visualise overall activation per condition in each age group (**figure 2**), two Condition versus Rest contrast images were made for each subject, which were subsequently subjected to a second level random effects analysis (one-sample t-test; every age group/ condition separately).

Figure 2
Brain regions activated during recall of environmentally-richly encoded object-location associations (first row) or recall of environmentally-poorly encoded object-location associations (second row) compared to rest condition (visual fixation) in Young participants (left columns) and Elderly participants (right columns). Activations are shown on an individual brain rendered in 3D; only significant clusters are shown (P<0.05 FWE corr.).



In the statistical analysis, relevant contrasts (each recall condition separate, no baseline) corresponding to the hypotheses were used to generate contrast images for each subject, which were subsequently subjected to a second-level random effects analysis (2 x 2 ANCOVA with Age as between-subject factor, and Condition as within-subject factor. Subject performance was a covariate, to control for group differences). Results from the random effects analyses were initially thresholded at T = 3.20 (P = 0.001, uncorrected) and the suprathreshold cluster-size was used as the test statistic. Only clusters significant at P < 0.05 corrected for multiple non-independent comparisons based on the family-wise error rate (Worsley, et al. 1996) are reported.

Results

Behavioural Experiment

Performance during recall of object location associations without a predefined recall order was well above chance level (11% = 1/9 items x 100%) in both groups and conditions (environmentally-rich, young: mean correct = 75.0%, SD = 23.1%, t_{11} = 9.6, $P < 0.0001$; environmentally-poor, young: mean correct = 69.8%, SD = 22.6%, t_{11} = 9.0, $P < 0.0001$; environmentally-rich, elderly: mean correct = 71.1%, SD = 22.5%, t_{11} = 9.3, $P < 0.0001$; environmentally-poor, elderly: mean correct = 64.2%, SD = 24.3%, t_{11} = 7.6, $P < 0.0001$). There was no interaction between age and condition ($F_{(1,22)}$ = 0.12, ns.) and no main effect of age on performance ($F_{(1,22)}$=0.26, ns.). Performance of both groups was better during recall after environmentally-rich encoding ($F_{(1,22)}$ = 6.40, $P < 0.05$).

To investigate whether participants used the spatial structure of the grid during retrieval after environmentally-rich or the environmentally-poor encoding, we analysed the relation between response order and positions in the grid of the correct answers only. For items encoded in a rich environment, the percentage of correct answers that were relocated in spatially contiguous (adjacent) positions in the grid during retrieval, was above chance level only in young participants (young: mean = 134%, SD = 28%; one-sample t-test, test value = 100%, $P < 0.01$; elderly: mean = 93%, SD = 26%, ns.). For items encoded in a poor environment, the percentage of spatial contiguous correct answers was not different from chance level in both groups (young: mean = 99%, SD = 44%, one-sample t-test, test value = 100%, ns; elderly: mean = 90%, SD = 39%, ns). This pattern of results indicates that the young used the environmental cues (neighbouring items) to reconstruct the grid after the environmentally-rich encoding condition.

fMRI Experiment

Behavioural results

During cued recall in the scanner, participants performed significantly above chance level (11%) in both groups (environmentally-rich condition, young: mean correct = 73.2%, SD = 16.2%, t_{19} = 17.2, $P < 0.0001$; environmentally-poor condition, young: mean correct = 66.7%, SD = 15.5%, t_{19} = 16.1, $P < 0.0001$; environmentally-rich, elderly: mean correct = 51.7%, SD = 16.8%, t_{19} = 10.8, $P < 0.0001$; environmentally-poor, elderly: mean correct = 44.3%, SD = 15.7%, t_{19} = 9.5, $P < 0.0001$). Young adults performed better than the elderly group ($F_{(1,38)}$ = 19.59, $P < 0.0001$). For both groups, performance was better for object-location associations that were studied in a rich than in a poor environment ($F_{(1,38)}$ = 43.27, $P < 0.0001$). No interaction between the factors age and condition was observed ($F_{(1,38)}$ = 0.16, ns.).

fMRI results

Given performance differences between young and old subjects, performance was used as a covariate in all fMRI analyses. However, not considering performance yielded very similar results (not shown) suggesting that differences in performance can hardly explain differences in brain activity observed between young and old subjects.

Cued recall versus rest and main effects

Following the two encoding conditions, young and elderly participants activated similar brain regions during cued recall relative to the visual fixation condition. In general, these involve the dorsal and ventral visual processing stream extending into the MTL, (pre)motor areas, dorsolateral prefrontal cortex (DLPFC) and the basal ganglia (see **figure 2**). Although the activation patterns from elderly appear generally more extensive compared to the young, a direct contrast between the two age groups shows only specific differences (see table 1). The left superior temporal lobe (BA 21/22/42) and right basal ganglia (caudate/putamen extending into insula) were stronger activated in elderly than in young participants (main effect of aging; Elderly>Young, in an Age x Condition ANCOVA, see **table 1**).

Condition x age interaction

To tackle the question at issue whether there are age-related differences in brain activity indicating compensatory processes we explored age-related differences in brain activation during retrieval between the environmentally-rich and environmentally-poor conditions by examining the interaction between the factors of condition and age. The Condition x Age interaction (Environmentally-rich > Environmentally-poor & Elderly>Young, **see table 1** and **figure 3**) revealed effects in the basal ganglia (left and right globus pallidus), thalamus, left fusiform gyrus, left middle temporal gyrus, right parahippocampal gyrus and right hippocampus. In particular the interaction in the basal ganglia and thalamus seems to be driven by stronger brain activation by the elderly after the environmentally-rich encoding condition (see **figure 3A** and **B**, for a graph of the parameter estimates). For instance, elderly have significantly stronger activation in the thalamus than the young after the environmentally-rich encoding condition (Post hoc two sample t-test: t_{38}= -2.1; $P<0.05$). In addition, activity in the thalamus is higher after environmentally-poor encoding than after environmentally-rich encoding in the young (one sample t-test: t_{19} = -2.3; $P<0.05$). In the elderly the reverse is the case (t_{19} = 3.4; $P<0.005$).

Table 1
Local maxima of the age x condition ANCOVA.

Main effect of age (ANCOVA: Elderly > Young)					
Region	**BA**	**Z score**	**Local Maxima**		
			x	**y**	**z**
STG (l)	21/22	4.12	-62	-8	6
STG (l)	42	4.03	-64	-20	8
Putamen		4.34	28	18	10
Insula		3.69	36	16	6
Caudate		3.50	20	22	2

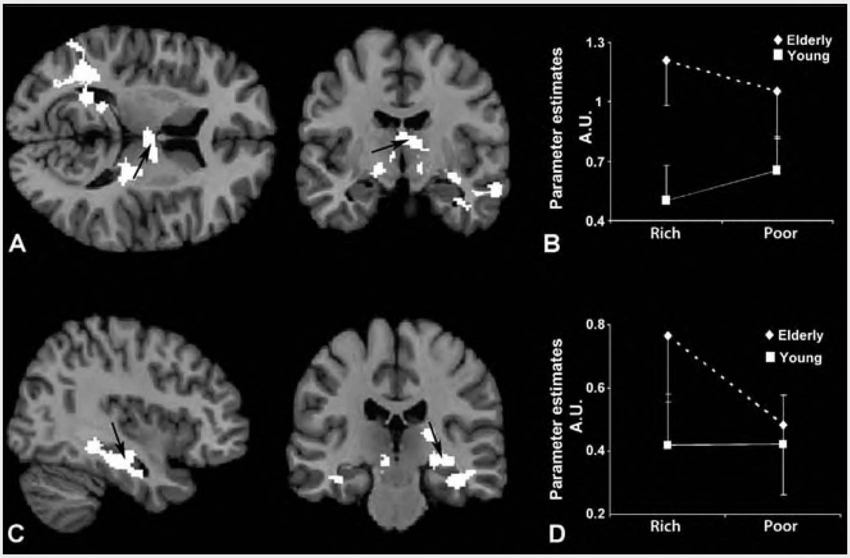
Interaction effect (ANCOVA: Environmentally-rich > Environmentally-poor & Elderly > Young)					
Region	**BA**	**Z score**	**Local Maxima**		
			x	**y**	**z**
MTG (l)		4.64	-40	-50	10
Fusiform gyrus (l)	37	4.15	-42	-48	-16
ITG (l)		4.03	-46	-50	-8
Thalamus (r)(pulv.)		4.43	22	-24	10
Parahippocampal gyrus (r)		4.27	38	-24	-20
Brainstem (r)		4.14	6	-40	-10
Internal capsule (l)		4.04	-16	-12	-8
Globus Pallidus (l)		3.86	-22	-18	-6
Thalamus (l) (lp)		3.58	-10	-16	-2
Thalamus (r) (dm)		3.88	4	-10	10
Thalamus (r) (nvl)		3.88	10	-8	4
Globus Pallidus (r)		3.59	18	-4	-6

Stereotaxic coordinates are listed in MNI space. BA = Brodmann area; pulv. = pulvinar; lp = lateral posterior nucleus; dm = mediodorsal nucleus; nvl = ventral lateral nucleus.

In addition, we found an interaction of the factors condition and age in an extended MTL region. To explore this further, we plotted the parameter estimates of the local maximum in the hippocampus ([28 -22 -6], **figure 3C** and **D**). Elderly showed enhanced activation compared to young during cued recall after environmentally-rich encoding (two sample t-test: $t_{38} = -2.4$; $P < 0.05$). Activation in elderly was also enhanced after the environmentally-rich encoding condition when compared with the environmentally-poor condition (one sample t-test: $t_{19} = 4.6$; $P<0.001$).

Altogether, generally increased activation during recall in fronto-striatal network and left superior temporal lobe is accompanied by enhanced activation of the declarative memory system in the elderly after environmentally-rich encoding.

Figure 3
Interaction effects (Environmentally-rich versus Environmentally-poor & Elderly versus Young), showing a transverse and a coronal view of the cluster of activation in the thalamus (A; z = 10 and y = -10) and a sagittal and coronal view of the cluster of activation in the right hippocampus/ parahippocampal gyrus (C; x = 38 and y = -24), indicated by arrows. Parameter estimates (in arbitrary units; A.U.) of the local maxima are shown in (B) ([x y z] = [4 -10 10]) and (D) ([x y z] = [28 -22 -6]). The parameter estimates show that the interaction effects are mainly driven by relatively enhanced activation in elderly during the recall of environmentally-richly encoded object-location associations. Activations are shown superimposed on a high resolution T1-weighted volume (rcolin.nii (Holmes, et al. 1998)). Error bars represent standard errors of the mean.



Discussion

In this study, we aimed to investigate the effects of aging on object-location memory and their neural underpinnings, by employing two complementary experiments (with identical encoding conditions) involving a task where the retrieval conditions differed only in the way the object-location associations were encoded. Because the test procedures within each experiment were identical for the two conditions at issue, the differences in brain activity or performance were exclusively related to differences occurring at encoding. In other words, one can conclude that differences in performance between conditions in the behavioural experiment are related to differences that occurred at encoding and that differences in retrieval-related activity between conditions in the imaging experiment are related to the very same differences that occurred at encoding.

Behaviourally, despite small subject groups, we found that young are able to use the information from an environmentally rich encoding structure systematically during retrieval; they used a representation likely to involve mental imagery after environmentally rich encoding. In contrast, environmental support does not result in the use of an imagery-based representation in elderly.

Both age groups benefited from the visibility of all neighbouring objects during the environmentally rich encoding condition, which is reflected by the increased performance on this condition in the behavioural and fMRI experiment. On the brain level, the enrichment of the encoding structure resulted in specific differences between young and elderly subjects. While in young it results in the use of imagery (cuneus) during recall (see De Rover, et al. 2008), the elderly engage their declarative memory system (hippocampus, thalamus, fusiform gyrus) to accompany the fronto-striatal network. In general, elderly showed enhanced activation of the basal ganglia (right caudate extending to insula), as we had expected.

During the fMRI experiment, the elderly were outperformed by the young. This is likely to be reflected in the main effect of aging that was observed in the left superior temporal gyrus. The elderly probably had difficulty suppressing task irrelevant input (such as scanner noise) (see also Amenedo and Diaz 1998, Meulenbroek, et al. 2004). This idea is in line with studies investigating effects of attention on visual processing (Gisselgard, et al. 2003, Petersson, et al. 1999, Rouleau and Belleville 1995), which showed that task-irrelevant processing can be suppressed by, for instance, deactivation of the auditory cortex. Hence, one might speculate that elderly participants have more difficulty focusing their attention on task-relevant visual input.

The putamen and caudate nucleus, in which also a main effect of age was observed, are in the literature often implicated in tasks where stimulus-response learning is involved (Knowlton, et al. 1996, Packard and Knowlton 2002). We therefore attribute this effect to the support that the fronto-striatal network gives to the declarative memory system, because attentional resources decline with age.

We observed several interaction effects, which indicate that environmental support results in involvement of the declarative memory system: The medial dorsal nucleus of the thalamus is thought to be involved in the strategic component of declarative memory (Aggleton and Brown 2006), as for instance lesions of the medial dorsal nucleus affect the ability to use retrieval strategies (for a review, see Van Der Werf, et al. 2003). Van der Werf and colleagues propose an important role of this nucleus in controlling focus on the memory content. With age, the thalamus seems to stay relatively preserved structurally (for example, see Grieve, et al. 2005). The differential activation we observed is therefore probably compensatory and specific, that is, it might be related to the retrieval of additionally encoded information (neighbouring items) in the condition where this information was given (environmentally-rich condition).

We also found an interaction effect in the right MTL. Several previous memory studies also observed enhanced activation of the right MTL in elderly (Maguire and Frith 2003, Meulenbroek, et al. 2004), which has generally been interpreted as additional spatial processing. No doubt the MTL is involved in spatial processing (Bird and Burgess 2008, Eichenbaum, et al. 1999), but this involvement is not exclusive. For instance, Ekstrom and Bookheimer (2007) observed the hippocampus is equally involved during spatial and sequential retrieval in young subjects. Furthermore, patients with MTL lesions perform poorly on memory tasks for spatial location, temporal order and list discrimination (for a review, see Yonelinas 2002). In addition, it was found that the hippocampus is involved in encoding of between-domain associations (Piekema, et al. 2009) and the maintenance of object-location associations (Piekema, et al. 2006). These data point to a more general function, namely, retrieval of contextual information. Importantly, young did not show differential activation in the MTL as a result of condition. We therefore think the interaction effect in the right MTL reflects support of the declarative memory system to the fronto-striatal network in the elderly, which is also in line with the observation of Voermans and colleagues (2004) that the hippocampus can compensate for reduced caudate processing when necessary. Future studies may aim to elucidate this finding.

The enhanced activation of the fusiform, middle and inferior temporal gyrus, can probably also be ascribed to the support of the declarative memory system (Cabeza and Nyberg 2000). Classically these areas are involved in object-recognition, identification and categorization (Kondo, et al. 2005, Martin and Chao 2001). Possibly, the enhanced activation found in the elderly only after environmentally rich encoding indicates the retrieval of information from neighbouring objects (such as "the adjacent objects were non-living"). This is, however, speculative and needs to be investigated further.

We are aware that the observed performance differences during the fMRI experiment pose a possible confounding effect on the interpretation of the data, especially regarding compensatory effects. The fact that the grid was not reconstructed over the course of the cued recall condition compromised the opportunity to benefit from environmental support. Within the concept of encoding specificity (Tulving and Thomson 1973), this means the retrieval cues were probably less effective in providing access to the stored information. In contrast to the task during fMRI, the behavioural experiment provided more overlap between study and test processing, helping retrieval. This concept is otherwise known as transfer appropriate processing (Morris, et al. 1977). Together with the time pressure, this is likely what caused the worse performance in the fMRI experiment in the elderly. Regardless, we think controlling the fMRI data on single-subject and group level for performance levels provided us with sufficiently corrected data.

Applying an associative memory task like ours will likely recruit prefrontal areas like DLPFC. In our study, retrieval of object-location associations compared to visual fixation did activate the DLPFC. However, no significant differences were observed in direct comparison of the recall conditions or the age groups. Probably both conditions engage the DLPFC to the same degree (De Rover, et al. 2008, Kessels, et al. 2007). The lack of an age-related difference in the DLPFC is more difficult to interpret. One might expect prefrontal activations in elderly to be less asymmetric because of recruitment of contralateral homologous structures, as was found by Cabeza in high-performing adults (Cabeza, et al. 2002) and subsequently interpreted in the HAROLD model (Hemispheric Asymmetry Reduction in Older adults) (Cabeza 2002). Some studies report under-recruitment of prefrontal areas in elderly (Grady, et al. 1995, Logan, et al. 2002), but then mostly during encoding. The present experiment, however, focuses on retrieval influenced by encoding structure. The most plausible explanation for the lack of differences in the DLPFC is that the demand on the DLPFC is equal across the groups.

In conclusion, our findings demonstrate that environmental support during encoding results in young in the use of imagery during recall, while elderly engage their declarative memory system in addition to the fronto-striatal network. In general, elderly try to solve the task by stimulus-response associations based on single trial learning, because they lack attentional resources.

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References

Aggleton, J.P. and Brown, M.W., 2006. Interleaving brain systems for episodic and recognition memory. Trends Cogn Sci 10, 455-63.

Amenedo, E. and Diaz, F., 1998. Effects of aging on middle-latency auditory evoked potentials: a cross-sectional study. Biol Psychiatry 43, 210-9.

Baddely, A., 1995. Working Memory. In The Cognitive Neurosciences. M. Gazzaniga ed., MIT Press, Cambridge, MA, pp. 755-764.

Bird, C.M. and Burgess, N., 2008. The hippocampus and memory: insights from spatial processing. Nat Rev Neurosci 9, 182-94.

Cabeza, R., 2002. Hemispheric asymmetry reduction in older adults: the HAROLD model. Psychol Aging 17, 85-100.

Cabeza, R., Anderson, N.D., Locantore, J.K. and McIntosh, A.R., 2002. Aging Gracefully: Compensatory Brain Activity in High-Performing Older Adults. NeuroImage 17, 1394-1402.

Cabeza, R., Daselaar, S.M., Dolcos, F., Prince, S.E., Budde, M. and Nyberg, L., 2004. Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. Cereb Cortex 14, 364-75.

Cabeza, R. and Nyberg, L., 2000. Imaging cognition II: An empirical review of 275 PET and fMRI studies. J Cogn Neurosci 12, 1-47.

Chalfonte, B.L. and Johnson, M.K., 1996. Feature memory and binding in young and older adults. Mem Cognit 24, 403-16.

Craik, F.I.M. and Byrd, M., 1982. Aging and cognitive deficits: The role of attentional resources. In Aging and cognitive processes. F.I.M. Craik and S. Trehub eds., Plenum, New York.

Craik, F.I.M., Byrd, M. and Swanson, J.M., 1987. Patterns of Memory Loss in Three Elderly Samples. Psychol Aging 2, 79-86.

Craik, F.I.M. and McDowd, J., 1987. Age differences in recall and recognition. J Exp Psychol Learn Mem Cogn 13, 474-479.

De Rover, M., Petersson, K.M., Werf, S.P.v.d., Cools, A.R., Berger, H.J. and Fernández, G., 2008. Neural correlates of strategic memory retrieval: Differentiating between spatial-associative and temporal-associative strategies. Hum Brain Mapp 29, 1068-1079.

Dunlosky, J. and Hertzog, C., 1998. Aging and deficits in associative memory: what is the role of strategy production? Psychol Aging 13, 597-607.

Eichenbaum, H., Dudchenko, P., Wood, E., Shapiro, M. and Tanila, H., 1999. The hippocampus, memory, and place cells: is it spatial memory or a memory space? Neuron 23, 209-26.

Ekstrom, A.D. and Bookheimer, S.Y., 2007. Spatial and temporal episodic memory retrieval recruit dissociable functional networks in the human brain. Learn Mem 14, 645-54.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-P., Frith, C.D. and Frackowiak, R.S.J., 1994. Statistical parametric maps in functional imaging: A general linear approach. Hum Brain Mapp 2, 189-210.

Gisselgard, J., Petersson, K.M., Baddeley, A. and Ingvar, M., 2003. The irrelevant speech effect: a PET study. Neuropsychologia 41, 1899-1911.

Glisky, E.L., Rubin, S.R. and Davidson, P.S., 2001. Source memory in older adults: an encoding or retrieval problem? J Exp Psychol Learn Mem Cogn 27, 1131-46.

Grady, C., McIntosh, A., Horwitz, B., Maisog, J., Ungerleider, L., Mentis, M., Pietrini, P., Schapiro, M. and Haxby, J., 1995. Age-related reductions in human recognition memory due to impaired encoding. Science 269, 218-221.

Grieve, S.M., Clark, C.R., Williams, L.M., Peduto, A.J. and Gordon, E., 2005. Preservation of limbic and paralimbic structures in aging. Hum Brain Mapp 25, 391-401.

Hayasaka, S. and Nichols, T.E., 2003. Validating cluster size inference: random field and permutation methods. Neuroimage 20, 2343-56.

Hedden, T. and Gabrieli, J.D., 2004. Insights into the ageing mind: a view from cognitive neuroscience. Nat Rev Neurosci 5, 87-96.

Holmes, C.J., Hoge, R., Collins, L., Woods, R., Toga, A.W. and Evans, A.C., 1998. Enhancement of MR images using registration for signal averaging. J Comput Assist Tomogr 22, 324-33.

Iaria, G., Petrides, M., Dagher, A., Pike, B. and Bohbot, V.D., 2003. Cognitive Strategies Dependent on the Hippocampus and Caudate Nucleus in Human Navigation: Variability and Change with Practice. J Neurosci 23, 5945-5952.

Ivry, R.B. and Spencer, R.M., 2004. The neural representation of time. Curr Opin Neurobiol 14, 225-32.

Jonker, C., Launer, L.J., Hooijer, C. and Lindeboom, J., 1996. Memory complaints and memory impairment in older individuals. J Am Geriatr Soc 44, 44-9.

Kausler, D.H. and Puckett, J.M., 1981. Adult age differences in memory for modality attributes. Exp Aging Res 7, 117-25.

Kessels, R.P.C., Hobbel, D. and Postma, A., 2007. Aging, context memory and binding: a comparison of „what, where and when" in young and older adults. Int J Neurosci 117, 795-810.

Knowlton, B.J., Mangels, J.A. and Squire, L.R., 1996. A neostriatal habit learning system in humans. Science 273, 1399-402.

Kondo, Y., Suzuki, M., Mugikura, S., Abe, N., Takahashi, S., Iijima, T. and Fujii, T., 2005. Changes in brain activation associated with use of a memory strategy: a functional MRI study. Neuroimage 24, 1154-63.

Logan, J.M., Sanders, A.L., Snyder, A.Z., Morris, J.C. and Buckner, R.L., 2002. Under-Recruitment and Nonselective Recruitment: Dissociable Neural Mechanisms Associated with Aging. Neuron 33, 827-840.

Maguire, E.A. and Frith, C.D., 2003. Aging affects the engagement of the hippocampus during autobiographical memory retrieval. Brain 126, 1511-1523.

Martin, A. and Chao, L.L., 2001. Semantic memory and the brain: structure and processes. Curr Opin Neurobiol 11, 194-201.

Mayes, A.R., Montaldi, D. and Migo, E., 2007. Associative memory and the medial temporal lobes. Trends Cogn Sci 11, 126-135.

McIntyre, J.S. and Craik, F.I., 1987. Age differences in memory for item and source information. Can J Psychol 41, 175-92.

Meulenbroek, O., Petersson, K.M., Voermans, N., Weber, B. and Fernandez, G., 2004. Age differences in neural correlates of route encoding and route recognition. Neuroimage 22, 1503-14.

Mitchell, K.J., Johnson, M.K., Raye, C.L. and D'Esposito, M., 2000. fMRI evidence of age-related hippocampal dysfunction in feature binding in working memory. Brain Res Cogn Brain Res 10, 197-206.

Morris, C.D., Bransford, J.D. and Franks, J.J., 1977. Levels of Processing versus Transfer Appropriate Processing. J Mem Lang 16, 519-533.

Naveh-Benjamin, M., 2000. Adult age differences in memory performance: Tests of an associative deficit hypothesis. J Exp Psychol Learn Mem Cogn 26, 1170-1187.

Naveh-Benjamin, M., Guez, J., Kilb, A. and Reedy, S., 2004. The associative deficit of older adults: Further support using face-name associations. Psychol Aging 19, 541-546.

Naveh-Benjamin, M., Hussain, Z., Guez, J. and Bar-On, M., 2003. Adult age differences in memory performance: Further support for an associative deficit hypothesis. J Exp Psychol Learn Mem Cogn 29, 826-837.

Naveh-Benjamin, M., Keshet Brav, T. and Levy, O., 2007. The associative memory deficit of older adults: the role of strategy utilization. Psychol Aging 22, 202-208.

Old, S.R. and Naveh-Benjamin, M., 2008. Differential effects of age on item and associative measures of memory: a meta-analysis. Psychol Aging 23, 104-18.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97-113.

Packard, M.G. and Knowlton, B.J., 2002. Learning and memory functions of the Basal Ganglia. Annu Rev Neurosci 25, 563-93.

Park, D.C. and Puglisi, J.T., 1985. Older adults' memory for the color of pictures and words. J Gerontol 40, 198-204.

Petersson, K.M., Elfgren, C. and Ingvar, M., 1999. Dynamic changes in the functional anatomy of the human brain during recall of abstract designs related to practice. Neuropsychologia 37, 567-587.

Petersson, K.M., Nichols, T.E., Poline, J.B. and Holmes, A.P., 1999. Statistical limitations in functional neuroimaging. II. Signal detection and statistical inference. Philos Trans R Soc Lond B Biol Sci 354, 1261-81.

Piekema, C., Kessels, R.P., Mars, R.B., Petersson, K.M. and Fernandez, G., 2006. The right hippocampus participates in short-term memory maintenance of object-location associations. Neuroimage 33, 374-82.

Piekema, C., Kessels, R.P., Rijpkema, M. and Fernandez, G., 2009. The hippocampus supports encoding of between-domain associations within working memory. Learn Mem 16, 231-4.

Poldrack, R.A. and Packard, M.G., 2003. Competition among multiple memory systems: converging evidence from animal and human brain studies. Neuropsychologia 41, 245-51.

Poldrack, R.A., Prabhakaran, V., Seger, C.A. and Gabrieli, J.D., 1999. Striatal activation during acquisition of a cognitive skill. Neuropsychology 13, 564-74.

Poldrack, R.A. and Rodriguez, P., 2004. How do memory systems interact? Evidence from human classification learning. Neurobiol Learn Mem 82, 324-32.

Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D. and Acker, J.D., 2005. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb Cortex 15, 1676-89.

Resnick, S.M., Pham, D.L., Kraut, M.A., Zonderman, A.B. and Davatzikos, C., 2003. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J Neurosci 23, 3295-301.

Rouleau, N. and Belleville, S., 1995. Aging and Inhibition - the Irrelevant Speech Effect. Brain Cogn 28, 200-201.

Schacter, D.L., Osowiecki, D., Kaszniak, A.W., Kihlstrom, J.F. and Valdiserri, M., 1994. Source memory: extending the boundaries of age-related deficits. Psychol Aging 9, 81-9.

Simons, J.S., Dodson, C.S., Bell, D. and Schacter, D.L., 2004. Specific- and partial-source memory: effects of aging. Psychol Aging 19, 689-94.

Snodgrass, J.G. and Vanderwart, M., 1980. A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. J Exp Psychol [Hum Learn] 6, 174-215.

Spencer, W.D. and Raz, N., 1995. Differential effects of aging on memory for content and context: a meta-analysis. Psychol Aging 10, 527-39.

Tulving, E. and Thomson, D.M., 1973. Encoding specificity and retrieval processes in episodic memory. Psychol Rev 80, 352-373.

Vakil, E., Kahan, S., Huberman, M. and Osimani, A., 2000. Motor and non-motor sequence learning in patients with basal ganglia lesions: the case of serial reaction time (SRT). Neuropsychologia 38, 1-10.

Van Der Werf, Y.D., Jolles, J., Witter, M.P. and Uylings, H.B.M., 2003. Contributions of Thalamic Nuclei to Declarative Memory Functioning. Cortex 39, 1047-1062.

Voermans, N.C., Petersson, K.M., Daudey, L., Weber, B., Van Spaendonck, K.P., Kremer, H.P. and Fernandez, G., 2004. Interaction between the human hippocampus and the caudate nucleus during route recognition. Neuron 43, 427-35.

Wegesin, D.J., Jacobs, D.M., Zubin, N.R., Ventura, P.R. and Stern, Y., 2000. Source memory and encoding strategy in normal aging. J Clin Exp Neuropsychol 22, 455-464.

Wheeler, M.E., Petersen, S.E. and Buckner, R.L., 2000. Memory's echo: vivid remembering reactivates sensory-specific cortex. Proc Natl Acad Sci U S A 97, 11125-9.

Worsley, K.J., Marrett, S., Neelin, P., Vandal, A.C., Friston, K.J. and Evans, A.C., 1996. A unified statistical approach for determining significant signals in images of cerebral activation. Hum Brain Mapp 4, 58-73.

Yonelinas, A.P., 2002. The Nature of Recollection and Familiarity: A Review of 30 Years of Research. J Mem Lang 46, 441-517.

4

Chapter

Autobiographical memory retrieval in patients with Alzheimer's disease

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Abstract

With aging, the content of self-reported autobiographical memories shifts from episodic to semantic. Onset of Alzheimer's disease enhances this pattern, but the neural underpinnings of this change in Autobiographical Memory (AM), in particular the role of hippocampal degradation, are unknown. We employed fMRI contrasting autobiographical and semantic retrieval, in 22 healthy elderly and 21 Alzheimer's patients. The shift towards semantic characteristics in AM retrieval was indeed enhanced in patients. Both groups activated brain regions commonly involved in AM retrieval, including occipital association areas, medial temporal lobes, lateral temporal and midline prefrontal areas. When compared to controls, Alzheimer's patients showed enhanced activity in the left inferior frontal gyrus (LIFG), ventromedial prefrontal cortex (vmPFC), right precuneus and left lingual gyrus. Activation of LIFG and vmPFC was significantly negatively correlated with hippocampal volume in patients only. Thus, we speculate that the linking function of the degraded hippocampus is taken over by the vmPFC; a shift recently observed during normal consolidation. This potentially compensatory process may support early Alzheimer's detection or prognosis.

Introduction

Various studies have focused on autobiographical memory (AM), identifying brain regions involved in remembering personal past experiences, including the hippocampus, medial and ventrolateral prefrontal cortices (PFC), medial and lateral temporal cortices, temporoparietal junction, retrosplenial (RSC)/ posterior cingulate cortex and cerebellum (Cabeza and St Jacques 2007, Conway et al. 2002, Maguire 2001, Svoboda et al. 2006).

The classical distinction of declarative memory into episodic and semantic elements (Tulving 1972) closely approximates AM content: semantic elements represent facts about the world and our life, unrelated to specific events (lacking contextual details). Conversely, episodic elements are unique and have associated contextual details, allowing for subjective re-experiencing («mental time travel», Tulving 2002). Semantic elements can probably guide the search to episodic elements, making recall of AM an iterative, hierarchical process, with left-lateralised search processes (supported by PFC) followed by recollection (hippocampus, RSC), subjective re-experiencing (supported by occipital areas) and self-referential processing (medial PFC) (Cabeza and St Jacques 2007, Conway, et al. 2002, Daselaar et al. 2008).

With aging, more semantic elements are reported per probed autobiographical memory, while the amount of episodic elements decreases, but the total number of details remains unaffected (Levine et al. 2002). Therefore, AM seems to "semanticize" with age, which could be related to faster decline of episodic than semantic memories (Piolino et al. 2002). In other words, semantic retrieval might compensate for episodic retrieval failure. Thus, it is not surprising that the episodic-to-semantic shift of AM becomes amplified with memory impairment, like amnestic Mild Cognitive Impairment (aMCI) (Murphy et al. 2008) and is probably further pronounced in Alzheimer's disease, but studies are lacking. This putatively compensatory mechanism is potentially detectable by fMRI and clinically relevant for early diagnosis. However, little is known about the neural correlates of AM retrieval in Alzheimer's patients. A neuropsychological study by Gilboa and coworkers (2005), correlating scores from the Autobiographical Memory Interview (Kopelman et al. 1990) with structural MRI, indicates where differences may be observed. Specifically, episodic scores of AM retrieval correlated positively with medial temporal lobe (MTL) volume. This corroborates the central role of the MTL in episodic memory retrieval (e.g. Squire et al. 1992), AM retrieval (Svoboda, et al. 2006) and Alzheimer's disease course (Chetelat et al. 2003, Killiany et al. 2000).

Indeed, the hippocampus is a core structure in AM retrieval, and its activation enhances with increasing vividness, independent of recency (Addis et al. 2004). This is consistent with the multiple trace theory of consolidation (MTT), stating that retrieval is accompanied by sustained hippocampal dependence of episodic elements like vividness (Moscovitch et al. 2006). Structural hippocampal degradation, a hallmark of Alzheimer's disease (Blennow et al. 2006, Braak et al. 1999), is therefore bound to have functional consequences on AM retrieval.

According to MTT, AM will be less dependent on the hippocampus when it contains fewer episodic elements, like with semantisation. Consequently, AM putatively becomes protected from the hippocampal damage in Alzheimer's disease. We therefore aimed to find neural evidence for increased semantic processing during AM retrieval in Alzheimer's patients. We specifically hypothesize that hippocampal volume (as a measure of disease severity) will be negatively correlated to activation in areas of compensation in these patients. In other words, the smaller the hippocampus, the larger the activation in these areas will be.

To test our hypotheses, we contrasted processing of autobiographical statements (derived from individual interviews) with a control condition, involving processing of matched semantic statements. This control was chosen, because it is commonly used as control in AM tasks (Addis et al. 2004, Addis et al. 2004, Levine et al. 2004, Maguire and Mummery 1999). We expect that the episodic-to-semantic shift in Alzheimer's patients leads to increased semantic processing and therefore enhanced activation of the left inferior frontal gyrus (LIFG), an area commonly involved in processing of language and world knowledge (Hagoort et al. 2004), during AM retrieval.

Semantic elements of autobiographical memories are probably very stable and can be regarded as well-consolidated (for a review on consolidation, see Frankland and Bontempi 2005). Retrieval of consolidated memories appears to involve the ventromedial PFC (vmPFC) (Takashima et al. 2006). Additionally in rodents, neural firing becomes selective for acquired memories (associations) during consolidation (Takehara-Nishiuchi and McNaughton 2008), and lesions of vmPFC cause a selective retrieval deficit for remote but not recent memories (Takehara et al. 2003). Hence, we expect that the episodic-to-semantic shift results in enhanced vmPFC activation during AM retrieval in Alzheimer's patients.

Materials and methods

Participants

Twenty-two healthy older adults (Mean age (SD)= 69.6 (8.6); years of education (SD)= 16.5 (3.2); 6 female) and 21 patients (Mean age (SD)= 72.4 (7.1); years of education (SD)= 16.1 (3.9); 9 female) diagnosed with early stage, probable Alzheimer's disease according to the research criteria from Dubois and colleagues (2007), who had a Clinical Dementia Rating (CDR)≤1, participated. Table 1 summarises the demographics and neuropsychological scores of participants. Exclusion criteria comprised: cerebrovascular disease (modified Hachinski score>4), depression (Geriatric Depression Scale; GDS>11), severe presbyacusis, claustrophobia, psychopharmacological drugs, low vision or metal implants. The local medical-ethics committee approved this study.

None of the healthy elderly had a history of neurological/psychiatric disease or used psychopharmacological drugs, reported subjective memory impairment or showed cognitive decline on the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) or the second story of the Wechsler Memory Scale–Revised (Wechsler 1987). Six of 28 healthy elderly were excluded: two because of depression/low vision; one left the study before scanning; three were excluded from analysis (performance below chance level N=2) or signal drop-out in the basal ganglia (N=1). All elderly participants were autonomous community dwellers: while mostly retired, all were active in cultural pursuits, continuing education or with responsibilities in various associations. All were right-handed according to the Edinburgh handedness index (Oldfield 1971).

Alzheimer's patients were recruited within three months from diagnosis from the Memory Clinic of the Alzheimer Centre at the Radboud University Nijmegen Medical Centre (N=19) and the Geriatrics department of the "Gelderse Vallei" hospital in Ede (N=2). Diagnosis was supported by neuropsychological tests, assessing overall cognitive functioning with the MMSE (Folstein, et al. 1975), working memory function using the Digit Span subtest of the Wechsler Adult Intelligence Test–Third Edition (WAIS-III) (Wechsler 1997), psychomotor speed and mental flexibility (as part of executive functioning) with the Trail Making Test (TMT) (Bowie and Harvey 2006), see table 1. The Rey Auditory Verbal Learning Test (RAVLT) functioned as an index of word-list learning, assessing immediate and delayed free recall and delayed recognition (Van der Elst et al. 2005). Test scores were classified as 'impaired' if they were more than 1.5 SD below the normative mean, corrected for age, education and sex (Lezak et al. 2004). The biomarker criterion for diagnosis of probable Alzheimer's disease (Dubois, et al. 2007) in this study was MTL atrophy determined by visual scoring (Scheltens et al. 1992), and/or abnormal cerebrospinal fluid (Hulstaert et al. 1999).

Fourteen of 35 Alzheimer's patients were excluded: low vision (N=1), three left the study before scanning and ten during analysis (performance below chance level: N=7, anxiety: N=1 or artefacts: N=2). All except one were right-handed according to the Edinburgh handedness index (Oldfield 1971).

Intake and autobiographical interview

At intake, informed consent according to the Declaration of Helsinki (Lynoe et al. 1991), neuropsychological data, and an autobiographical interview (as basis for fMRI stimulus design) were obtained. Patients were accompanied by proxy. After administration of the WMS-R (Wechsler 1987) second story, the MMSE (Folstein, et al. 1975) and GDS (Yesavage et al. 1982), participants were comfortably seated in a living room-like setting (without proxy) for the interview.

Participants were instructed that the interview's purpose was to get a detailed account of memories (time/place specific) from their past. An overview of big life events (e.g., marriage, birth of children), made at the beginning, functioned as guideline. The interview (earliest memory to present) lasted until enough memories were gathered (approximately three hours), while participants were encouraged to report as many details as possible. When no specific event could be remembered, the life-events list from the Autobiographical Interview Administration Manual (belonging to Levine, et al. 2002) was given to the participant. The interview was semi-structured and corresponded to the "recall" and "general probe" condition from Levine (2002) combined. Records of the interviews were transcribed subsequently.

Table 1
Demographic data and behavioral results of the Healthy elderly and Alzheimer's patients.

Demographic characteristics	**Healthy Elderly (N=22)**		**Alzheimer's patients (N=21)**	
	Mean	***SD***	***Mean***	***SD***
Age	69.6	8.6	72.4	7.1
Sex (male/total)	16/22		12/21	
Education (years)	16.5	3.2	16.1	3.9

Neuropsychological test performance for diagnosis						
	Healthy Elderly (N=22)			Alzheimer's patients (N=21)		
Test	*Mean*	*SD*	*# impaired*	*Mean*	*SD*	*# impaired*
MMSE	*NA*			24.8	3.4	12
Digit Span (WAIS-III)	*NA*					4
Forward				8.4	2.2	
Backward				5.2	1.9	
RAVLT	*NA*					
Immediate recall				25.0	7.0	15
Delayed recall				2.6	1.7	18
Delayed recognition				24.2	3.7	15
TMT	*NA*					
Part A				61.8	38.9	5
Part B				157.8	80.8	8

Neuropsychological test performance during intake						
	Healthy Elderly (N=22)			Alzheimer's patients (N=21)		
Test	*Mean*	*SD*	*# impaired*	*Mean*	*SD*	*# impaired*
MMSE	29.0	1.1	0	25.3***	3.2	12
WMS-R Logical Memory II Delayed	11.8	3.9	0	4.3***	5.0	15
GDS	2.6	3.1		3.8	2.4	

Performance during fMRI scan				
	Healthy Elderly (N=22)		Alzheimer's patients (N=21)	
	Mean	*SD*	*Mean*	*SD*
Condition AM	84.0	8.5	73.5***	8.8
Hitrate	0.9	0.1	0.9	1.0
False Alarm rate	0.3.	0.2	0.5*	0.3
Condition Semantic	90.5	8.0	75.1***	13.0
Hitrate	1.0	0.1	0.8***	0.1
False Alarm rate	0.2	0.2	0.3	0.3
Mean memory rating	12.1	1.5	10.1***	2.1

Note. MMSE = Mini-Mental State Examination; WAIS-III = Wechsler Adult Intelligence Scale – Third Edition; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test; WMS-R = Wechsler Memory Scale – Revised; GDS = Geriatric Depression Scale; *** P<.0001; *P<.05. Number of impaired were based on available normative data for the memory tests.

Interview scoring procedure

Two researchers independently scored transcripts according to the Autobiographical Interview Scoring Manual (belonging to Levine, et al. 2002) on place/time localization, perceptual richness, emotions/thoughts, time integration and episodic richness. The maximum score of a memory was 21 points (3 points each, except for 6 points for episodic richness), resulting in a mean memory rating, reflecting the amount of episodic re-experiencing per participant. For an example, see figure 1.

Figure 1

Scoring example of a healthy older participant. This memory was scored as follows:
Main event: Meeting interpreter at the station.
Internal details: event = 4, place = 3, time = 4, perception (Percep) = 8, thought/emotion (T/Em) = 2; external details: external (Ext.) event = 0, semantic = 1, repetitions = 3, other = 0; ratings: place = 2/3 (larger scale information, lacking specific context), time = 2/3 (four pieces of time information, lacking specific context), perception = 3/3 (eight perceptual details, richly described), thought/emotion = 2/3 (response partially captures cognitive/emotional state at the time of the event), episodic richness = 3/6 (response had moderate detail but fell short of a rich re-lived description), time integration = 2/3 (a few details were given about a larger time frame, but lacked a fuller description).
The statement that was presented to the participant in the scanner: “You arrived in Wolokda and met a beautiful interpreter”.

Event Place Place Semantic
I went on a business trip to Wolokda, Russia. I only knew Russia and Russian
Event
women from pictures of the cold war. I was going to meet my interpreter at the
Place Event Time Emo/Th Percep Percep
station. As I arrived that morning, I saw this beautiful young woman, around 20
Percep Percep Percep
years old, with pitch blond hair, a fur cap and an awesome figure. I had never
Emo/Th Percep Percep
expected that. She could speak English and German, and had a chauffeur. Who
Rep Time
could ever expect to arrive on a Sunday morning in Russia, encounter a beautiful
Percep Time
woman who addresses you in English and German? It was cold, January and I
Rep
only knew Russian women from pictures where you see them sweeping the snow
Rep Time Event
off the street. It must have been January ’95, I was alone on a small business trip.

Additionally, memory details were divided into "internal" or "external", with internal details pertaining directly to the main event described. These reflect episodic re-experiencing, as they were time/place specific. Internal details contained five sub-categories: (1) event (happenings, unfolding of the story), (2) place, (3) time, (4) perceptual (sensory information like sights or sounds) and (5) emotions/thoughts. External details pertained to extraneous information not uniquely specific to the main memory described. Sub-categorisation included the previous five episodic categories, supplemented with: (6) semantic (general facts/knowledge related to the context of the event), (7) repetition and (8) other (e.g. metacognitive statements).

Details were tallied and summed: the internal-to-total ratio indicated the proportion of details per memory reflecting episodic re-experiencing unbiased by total verbal output.

Scores were entered in a multivariate ANOVA with Group as between-subjects factor (two levels) and Detail-category as within-subjects factor (thirteen levels), testing for interaction, main effects and between-subject effects. Results were corrected for multiple comparisons using Bonferroni correction. Alpha was set at 0.05.

For each participant, the most salient (highest amount of details and place/time specific) autobiographical memories distributed evenly over the lifetime were chosen to create 24 subject-unique stimuli (statements) for fMRI. On average, one memory served as the basis for 1.5±0.5 statements (Healthy participants: 1.2±0.2 statements/memory; Patients: 1.7±0.5; t_{41}=-4.43 $P<0.0001$), with a maximum of four distinct statements per memory.

fMRI: Stimulus material and experimental procedure

At least six weeks after the interview, participants returned for fMRI. All statements were randomised within condition (and therefore, there was no chronological order) and divided into eight blocks of three statements per condition. This means there was no chronological order in the autobiographical statements being presented. Condition blocks alternated (A, S, A, etc) and were separated by a 300ms white fixation cross. Condition order was counterbalanced over participants. Each statement was presented in white against a black background for 8s, followed by a 300ms white fixation cross, resulting in a 24.6s block length. Each statement was spread over three lines which were simultaneously presented in the centre of the screen, to minimize head movement. Above, "True/False?" was shown in yellow. We used Presentation software (www.neurobs.com) to present stimuli and record button presses. Stimuli were back-projected via an LCD-projector onto a translucent screen that participants viewed through a mirror on the head coil. The participant's head was immobilised to reduce motion.

Participants indicated by button press if each statement was true or false (true: false ratio = 3:1). For example: "All your colleagues watched as you arrived on a scooter on your first day at work" (true), "All your colleagues watched as you arrived on a bicycle on your first day at work" (false). Autobiographical statements (A) were matched for grammar, word frequency and number of syllables with 24 semantic statements (S), to prevent differences in semantic processing. For example: "Snoopy is a cartoon about a white dog" (true), "Snoopy is a cartoon about a white cat" (false).

Before going into the scanner, participants were extensively instructed and trained with two supplementary statements (i.e. statements that were not used in the actual experiment) for each condition. Participants had already visited the MRI suite during intake, familiarising them with the experimental setup. For the autobiographical condition, participants were instructed to read and subsequently recollect, i.e. "subjectively re-experience", (part of) the episode described to judge truthfulness. For the semantic condition, participants were instructed to read the statement and judge without relying on autobiographical events.

Data acquisition

Whole head T2*-weighted EPI-BOLD fMRI data were acquired with Siemens Sonata (12 healthy elderly, 9 patients) and Avanto (10 healthy elderly, 12 patients) 1.5T MR scanners using an interleaved slice acquisition sequence (TR= 2.27s, TE= 30ms, 90° flip-angle, 33 axial slices, slice-matrix size= 64x64, slice thickness= 3.5mm, no gap, FOV= 224mm, isotropic voxel-size= 3.5x3.5x3.5mm^3). High-resolution structural MR images were acquired with a T1-weighted MP-RAGE sequence (TR= 2.25s, TE= 3.93ms, 15° flip-angle, 176 sagittal slices, slice-matrix size=256x256, slice thickness= 1mm, voxel-size= 1x1x1mm^3).

MR Image preprocessing and statistical analysis

Image preprocessing and statistical analysis was done with SPM5 software (www.fil.ion.ucl.ac.uk). Functional EPI-BOLD images were realigned and subject-mean functional MR images were co-registered with the corresponding structural images using mutual information optimization. These were subsequently normalised (i.e., the normalisation transformations from the structural were applied to the functional images) and transformed into standardised MNI space defined by the MNI T1 template, and finally smoothed with an 8 mm Gaussian filter kernel (Hayasaka and Nichols 2003, Petersson et al. 1999). Preprocessing was inspected visually to verify if the co-registration and normalisation procedure worked properly and check realignment parameters. The fMRI data were proportionally scaled to account for global effects and analyzed statistically using the general linear model and statistical parametric mapping (Friston et al. 1994). The linear model included explanatory variables (box-car regressors), convolved with the canonical hemodynamic response function, modelling the experimental conditions in a blocked fMRI design. The realignment parameters were added as regressors of no-interest. A temporal high-pass filter of 128s was applied to account for various low-frequency effects. Contrasts (each condition versus an implicit baseline) for each participant were subjected to a second-level, random effects 2x2 ANCOVA, with Group as between-subject factor and Condition (AM or semantic: semantic being the control) as within-subject factor. Task performance (percentage), scanner, age of participant, mean memory rating (episodic re-experiencing score) and gender were included as covariates. Results of the random effects analysis were thresholded initially at $P=0.001$ (uncorrected) and then the cluster-size statistics were used as the test statistic at $P<0.05$ (corrected). Parameter estimates of significant clusters were extracted using Marsbar software (0.41, http://marsbar.sourceforge.net).

To determine total hippocampal volume (in mm^3) per participant, the structural MRI underwent automatic segmentation of subcortical structures with FSL4.1 FIRST v1.1 (Analysis Group, FMRIB, Oxford, UK) (Smith et al. 2004, Woolrich et al. 2009). This method is based on Bayesian statistical models of shape and appearance for subcortical structures from 317 manually labeled T1-weighted MR images (including brains from older persons and Alzheimer patients). To fit the models, the probability of the shape given the observed intensities is used (Patenaude 2007). After segmentation, volumes were calculated using a script in Matlab7.2 (MathWorks; Natick, MA, USA). Only boundary corrected data were used. Visual inspection of the segmented structures projected onto the T1-weighted MRI scans was done using MRIcroN Beta 7 (www.mricro.com/mricron), to check if the segmented structures align with the same structures on the T1. One dataset was removed (failed segmentation).

Absolute total hippocampal volumes were transferred to SPSS 15.0 for Windows (Lead Technologies Inc. SPSS Inc., Chicago, Illinois, USA) and subjected to a partial correlation analysis (one-tailed) with the extracted parameter estimates of significant clusters from the Patients>Healthy elderly (Autobiographical>Semantic) contrast from the fMRI analysis, while controlling for Brain Parenchymal Fraction (BPF: Juengling and Kassubek 2003). BPF (gray matter + white matter)/ intracranial volume) is a measure of global brain atrophy, and therefore, any effects found will be specific to hippocampal atrophy. To determine gray matter, white matter and csf volume for calculation of BPF, the structural MR images were segmented into gray matter, white matter, and cerebrospinal fluid with the VBM toolbox in SPM using priors (default settings).

Results

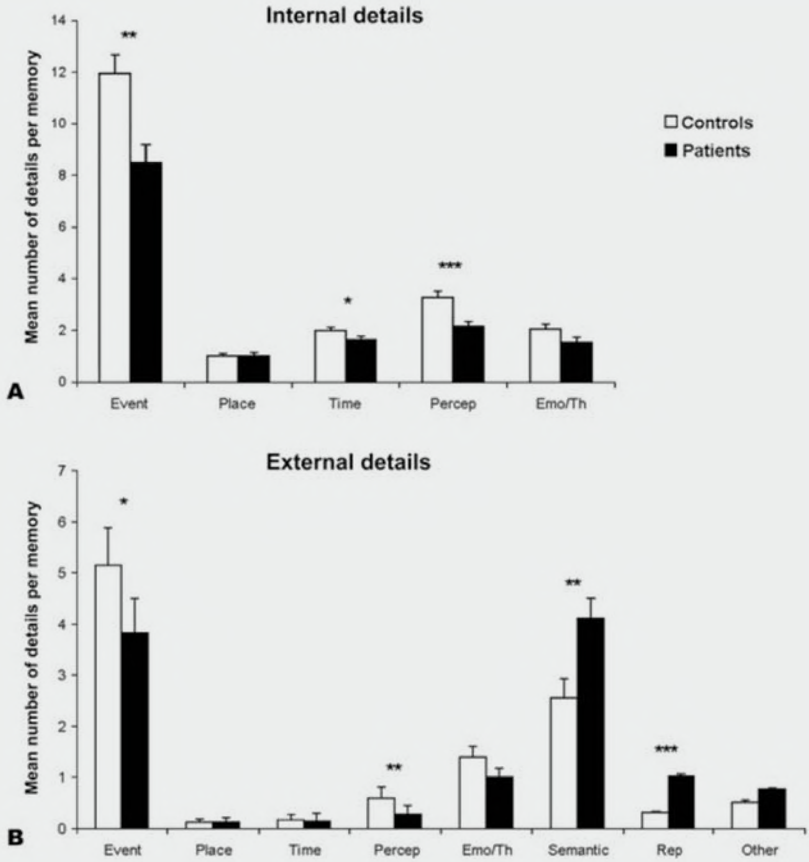
Behavioural results: autobiographical interview

Compared to healthy elderly, Alzheimer's patients showed a shift from episodic to semantic elements in their autobiographical narratives (see **figure 2**). Alzheimer's patients and healthy elderly produced autobiographical memories of similar length (Mean number of words per memory (SD): Healthy elderly 302 (59); Patients 262 (76); $F_{(1,41)}$= 3.65, ns.), indicating no difference in fluency.

On average, healthy elderly reported 20.4 ± 3.9 internal details and 10.9 ± 2.9 external details (not including semantic/repetitions/other). Patients reported 14.9 ± 4.6 internal details and 11.3 ± 2.5 external details. There was a significant Group x Detail interaction ($F_{(12,30)}$= 10.63, $P<0.001$) and a main effect of Group ($F_{(12,30)}$= 7.33, $P<0.05$) and a main effect of Detail ($F_{(12,30)}$ = 148.42, $P<0.001$). Post-hoc tests revealed that Alzheimer's patients reported less internal (episodic) details per memory regarding event (Mean (SD): Healthy elderly: 11.9 (3.5); Patients: 8.5 (3.2); $F_{(1,41)}$= 11.60, $P<0.005$), time (Mean (SD): Healthy elderly: 2.0 (0.5); Patients: 1.6 (0.7); $F_{(1,41)}$= 4.22, $P<0.05$) and perceptual information (Mean (SD): Healthy elderly: 3.3 (1.0); Patients: 2.2 (0.9); $F_{(1,41)}$= 14.67, $P<0.0005$) (see also **figure 1A**). There were no differences in amount of place (Mean (SD): Healthy elderly: 1.0 (0.3); Patients: 1.0 (0.4); $F_{(1,41)}<0.01$ ns.) and emotional details (Mean (SD): Healthy elderly: 2.0 (1.0); Patients: 1.6 (0.8); $F_{(1,41)}$= 3.27, ns.). This indicates the decrease in episodic re-experiencing in Alzheimer's patients is specifically pronounced in general event, time and perceptual elements.

Regarding external (episodic) details, Alzheimer's patients reported less event (Mean (SD): Healthy elderly: 5.2 (1.7); Patients 3.8 (1.9); $F_{(1,41)}$= 5.90, $P<0.05$) and perceptual (Mean (SD): Healthy elderly: 0.6 (0.4); Patients: 0.3 (0.2); $F_{(1,41)}$= 11.53, $P<0.01$) information per memory (see **figure 1B**). No differences were observed in the number of place

Figure 2
Mean number of details per memory of Healthy elderly (Controls) and Alzheimer's patients, divided into Internal (A) and External (B) details. Percep = Perceptual, Emo/th = Emotional/thoughts, Rep = Repetitions. *** P<.001; **P<.01; *P<.05.



(Mean (SD): Healthy elderly: 0.1 (0.1); Patients: 0.1 (0.2); $F_{(1,41)}$= 0.06, ns.), time (Mean (SD): Healthy elderly: 0.2 (0.2); Patients: 0.1 (0.2); $F_{(1,41)}$= 0.55, ns.), and emotional details (Mean (SD): Healthy elderly: 1.4 (0.7); Patients: 1.0 (0.7); $F_{(1,41)}$= 3.62, ns.). This indicates the decrease in episodic re-experiencing in Alzheimer's patients is also pronounced in their description of events and perceptions that were not uniquely pertaining to the main event described.

Alzheimer's patients report on average more semantic (Mean Semantic (SD): Healthy elderly: 2.6 (1.3); Patients: 4.1 (1.5); $F_{(1,41)}$= 13.15, P<0.01) and repetitive (Mean Rep (SD): Healthy elderly: 0.3 (0.3); Patients: 1.0 (0.7); $F_{(1,41)}$= 17.91, P<0.001) information (see also **figure 1B**). No differences were observed between the group regarding other statements (Mean Other (SD): Healthy elderly: 0.5 (0.3); Patients: 0.8 (0.7); $F_{(1,41)}$= 2.27, ns.).

The internal-to-total ratio in Alzheimer's patients was lower than in healthy elderly (Mean (SD) Healthy elderly 0.7 (0.1); Patients: 0.6 (0.1); $F_{(1,41)}$= 27.85, P<0.0001). Additionally, autobiographical memories from Alzheimer's patients received a lower mean memory rating than from healthy elderly (Mean (SD) Healthy elderly: 12.1 (1.5); Patients: 10.1 (2.1); $F_{(1,41)}$= 18.37, P<0.001). These results indicate that the autobiographical memories from healthy elderly were richer in episodic detail.

In conclusion, a whole set of behavioural measures confirms that autobiographical memories reported by Alzheimer's patients show an episodic-to-semantic content shift compared to healthy elderly.

Behavioural results: fMRI

Healthy elderly outperformed the Alzheimer's patients on both the autobiographical and the semantic condition (Mean Autobiographical (SD): Healthy elderly: 84.0 (8.5%); Patients: 73.5 (8.8%); $F_{(1,41)}$= 15.89, P<0.001; Semantic: Healthy elderly: 90.5 (8.0%); Patients: 75.1 (13.0%); $F_{(1,41)}$= 21.88, P<0.001). No main effect of condition or interaction was found (see table 1). Upon asking, none of the participants reported thinking about the interview during scanning.

Hippocampal volume

Alzheimer's patients had smaller hippocampi than healthy elderly (Mean mm^3 (SD): Healthy elderly: 5.7 (0.82 mm^3); Patients: 5.2 (0.8 mm^3); t_{40}= 2.02, P<0.05). These values roughly correspond in healthy elderly to a medial temporal lobe atrophy (MTA) score (Scheltens, et al. 1992) of 0-1 and in Alzheimer's patients to an MTA score of 1-2 (Knoops et al. 2009).

fMRI

AM retrieval (compared to semantic retrieval) activated a widespread set of brain regions, including occipital association areas, the medial temporal lobes, lateral temporal and prefrontal areas along the midline. These areas have previously been implicated as the core AM network (Cabeza and St Jacques 2007, Svoboda, et al. 2006).

Table 2
Functional MRI results.

Healthy elderly (Autobiographical > Semantic)						
Region	**Brodmann Area**	**Size**	**Z**	**Local maxima MNI coordinates**		
				x	**y**	**z**
Precuneus (l)/ RSC	7/23/31	3480	6.97	-8	-58	32
Middle temporal gyrus (l)	21/22	2095	5.88	-62	-36	-6
Angular gyrus (l)	39/19	1903	5.83	-46	-68	24
Frontal midline	9/10/11/12/32	2043	5.56	-6	60	-10
Angular gyrus (r)	39	694	4.90	46	-76	30
Middle temporal gyrus (r)	21/22	371	4.43	58	-12	-18
Caudate nucleus (l)		630	4.42	-10	-6	14
Hippocampus (l)		213	4.18	-24	-10	-14

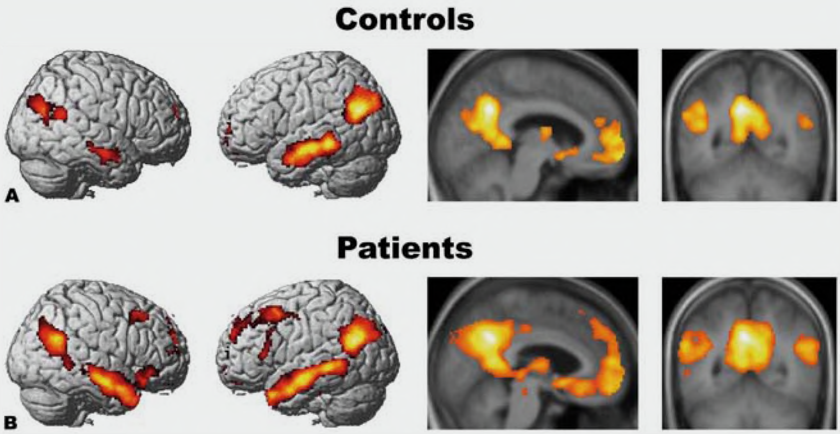
Patients (Autobiographical > Semantic)						
Region	**Brodmann Area**	**Size**	**Z**	**Local maxima MNI coordinates**		
				x	**y**	**z**
Precuneus (l)/ RSC Retrospl. cortex	7/23/31/29/32	15230	7.84	-4	-58	32
Frontal midline	9/10/11/12/25					
Hippocampus (l+r)						
Caudate (l)						
Middle temporal gyrus (r)	21/22/38	2044	6.01	64	-8	-18
Middle temporal gyrus (l)	21/22/38	3052	6.00	-62	-8	-16
Angular gyrus (l)	39/19	2213	5.98	-48	-68	24
Angular gyrus (r)	39	1372	5.51	50	-56	22
DLPFC (r)	9	383	4.95	28	22	46
IFG (r)	44/45	386	4.12	54	36	-8

Patients > Healthy elderly (Autobiographical > Semantic)						
Region	**Brodmann Area**	**Size**	**Z**	**Local maxima MNI coordinates**		
				x	**y**	**z**
IFG (l)	44/45	531	4.58	-44	20	20
Precuneus (r)	7	164	4.44	16	-54	42
Lingual gyrus (l)	18	259	4.32	-30	-74	-6
vmPFC	12	115	4.16	0	26	-18

Note. RSC= Retrosplenial Cortex; DLPFC= Dorsolateral Prefrontal Cortex; IFG= Inferior Frontal Gyrus; vmPFC= ventromedial Prefrontal Cortex; (l)= left; (r)= right.

4

Figure 3
Brain regions activated during autobiographical retrieval compared to semantic retrieval in (A) Healthy elderly (Controls) and (B) Alzheimer's patients. Activations are shown on an individual brain rendered in 3D; only significant clusters are shown (P<.05 FWE corr.).



For an overview, see figure 3 and table 2. The opposite contrast (Semantic versus Autobiographical retrieval) revealed no significant activations.

Turning to the analysis of main interest, Alzheimer's patients, compared to healthy elderly, displayed enhanced activation of the vmPFC, the LIFG, right precuneus and left lingual gyrus during autobiographical memory retrieval when compared to semantic retrieval. See figure 4.

A correlation analysis showed that across the Alzheimer's patients, the activity in the vmPFC and LIFG increased when hippocampal volume decreased (vmPFC: $r = -0.38$, $P<0.05$; LIFG: $r = -0.40$, $P<0.05$ (see **figure 5**).

The opposite contrast (healthy elderly versus patients) revealed no significant activations.

Figure 4
Brain regions showing enhanced activation in Alzheimer's patients versus Healthy elderly (Controls), in the Autobiographical>Semantic contrast. (A) vmPFC: x = 0 , (B) right precuneus: x = 16, (C) LIFG and (D) left lingual gyrus. Extracted parameter estimates (in arbitrary units; A.U.) of the clusters are shown alongside the images. Error bars represent standard errors of the mean. (A) and (B) are projected on the sagittal view of the mean normalised T1-image of all participants. (C) and (D) are shown on an individual brain rendered in 3D. Only significant clusters are shown (P<.05 FWE corr.).

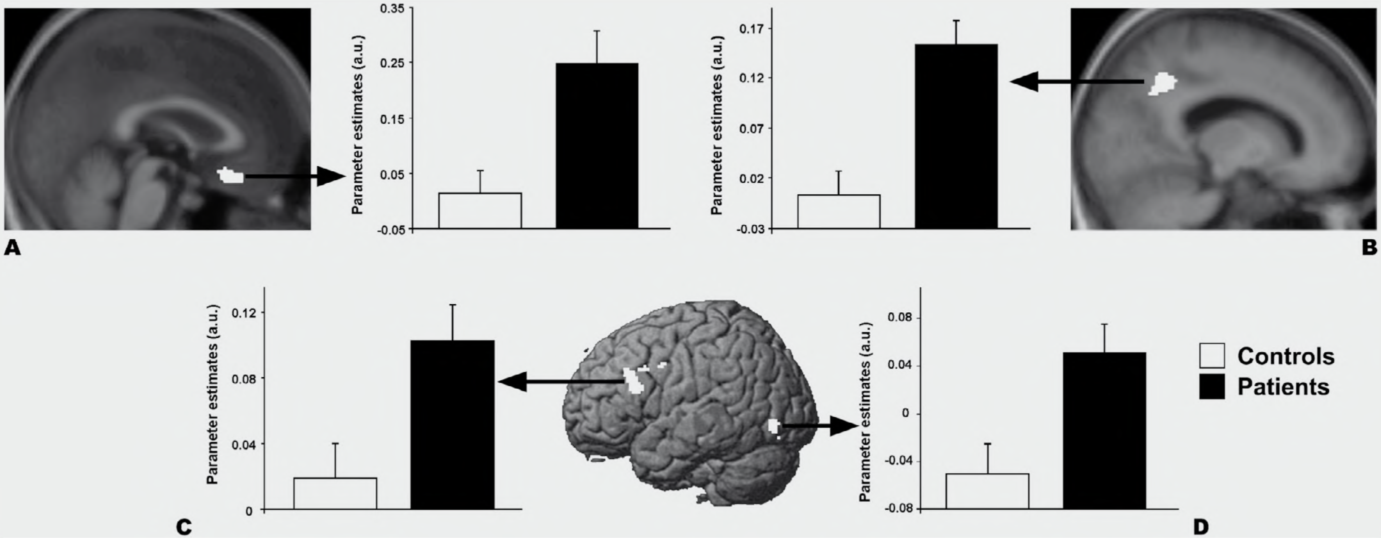
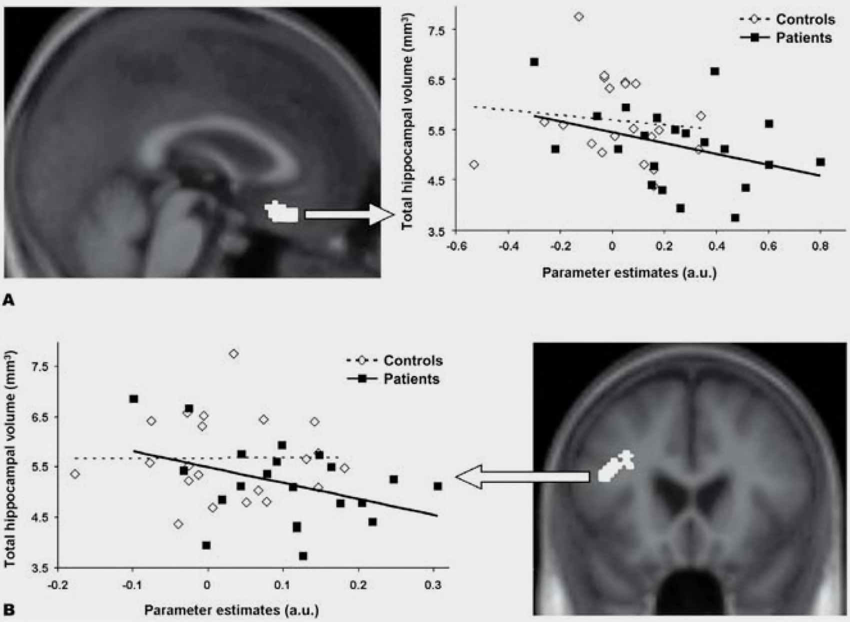


Figure 5
Scatter plots of extracted cluster parameter estimates (in arbitrary units; A.U.) of (A) vmPFC: x = 0, and (B) LIFG: y = 20, related to total hippocampal volume (mm3). Only in Alzheimer's patients, there is a significant negative correlation between activation in vmPFC (r = -0.37) or LIFG (r = -0.40) and total hippocampal volume, indicating enhanced activation of these areas during autobiographical retrieval with structural degradation of the hippocampus.



Discussion

Our study shows that AM in Alzheimer's patients has undergone an episodic-to-semantic content shift compared to healthy elderly. When probed with semantic or autobiographical statements during fMRI, healthy elderly outperformed the patients, corroborating the decline of autobiographical and semantic memory in Alzheimer's disease. Independent of performance, Alzheimer's patients displayed enhanced activation of vmPFC, LIFG, right precuneus and left lingual gyrus during retrieval of episodic elements of AM compared to healthy elderly. Moreover, increased activation of vmPFC and LIFG was correlated with structural hippocampal decline observed in the patients, indicating a potential compensatory mechanism.

The data from the autobiographical interview extend the data of Murphy and colleagues (2008) and Levine (2002) in that the episodic-to-semantic shift of AM observed in aging becomes exaggerated with Alzheimer-type dementia. Additionally, our study reveals specific differences in neural correlates of AM between Alzheimer's disease and healthy aging.

Firstly, Alzheimer's patients displayed enhanced activation of the LIFG, which is consistent with our hypothesis that patients would show enhanced semantic processing as a consequence of semantisation (for reviews on the role of LIFG in semantic processing, see Cabeza and Nyberg 2000, Thompson-Schill 2003). In the memory domain, LIFG has been implicated in post-retrieval selection (Badre and Wagner 2007), since its activity increases with increasing number or strength of retrieved competitors (Badre and Wagner 2005). This denotes a selection process that focuses attention on the essential details to reach task goal (true/false judgement) and indicates this selection process might be enhanced in Alzheimer's patients, reflecting compensation. Indeed, activation of LIFG correlates positively with memory performance of Alzheimer's patients (Grady et al. 2003) and moreover, a recent meta-analysis showed Alzheimer's patients displayed increased activation of bilateral IFG during retrieval in various memory tasks when compared to healthy elderly (Schwindt and Black 2009). For the right IFG, an inverse relationship with MTL activity was observed at successful recognition in young subjects and healthy elderly (Grady et al. 2005). The enhanced activation in Alzheimer's patients in our study is therefore likely compensatory for the reduction in episodic richness. This conclusion is strengthened by the correlation we observed with the hippocampal degradation, because hippocampal volume is related to episodic content of AM (Gilboa, et al. 2005), which is reduced in our Alzheimer's patients.

Secondly, Alzheimer's patients showed enhanced activation of the vmPFC compared to healthy elderly. In AM studies (Cabeza and St Jacques 2007, Gilboa 2004, Piefke et al. 2003, Summerfield et al. 2009, Svoboda et al. 2006), its activation is mostly attributed to monitoring or "feeling of rightness" (Moscovitch and Winocur 2002), since lesions cause confabulation (Curran et al. 1997, Gilboa et al. 2006, Johnson and Raye 1998, Parkin et al. 1996, Schacter et al. 1996, Verfaellie et al. 2004). Importantly, retrieval activation in vmPFC increases while activation of the hippocampus decreases with consolidation in humans (Takashima, et al. 2006) and rodents (Bontempi et al. 1999, Takehara-Nishiuchi and McNaughton 2008). Also, lesions in rodents cause a selective memory deficit for remote but not recent memories (Akirav and Maroun 2006, Takehara, et al. 2003). These studies indicate that the initial linking of neocortical representations by the hippocampus is passed to the vmPFC, suggesting close interaction with the hippocampus during consolidation (for a review on transformation of memories to cortical networks, see Frankland and Bontempi 2005, but see also van Kesteren et al. 2010). The intricate connections between the vmPFC and MTL support this view (Petrides and Pandya 2002). One might consider that the linking function of the hippocampus is related to vivid, episodic retrieval and the linking function of the vmPFC is related to semantic retrieval. Following that line of thought, semantisation of autobiographical memories will be reflected by a shift in the balance between hippocampus and vmPFC towards the vmPFC. This shift is especially pronounced in Alzheimer's patients, since their episodic retrieval deficit (caused by hippocampal damage) probably causes semantic retrieval to come into the limelight. But, since no decrease in hippocampal activation was observed in the Alzheimer's patients in this study, this parsimonious explanation is indirect.

We are intended to speculate that the correlations found between the hippocampal degradation and activation of LIFG and vmPFC point to compensatory processes in Alzheimer's patients (Reuter-Lorenz and Lustig 2005). However, we can only speak of a possible attempt to compensate, since performance of the patients is lower than that of the healthy elderly. Perhaps these processes can already be observed at an earlier stage when performance is not (yet) reduced and the hippocampus is still macroscopically intact, making them ideally suited as early markers. Future studies need to support these speculations.

The results on the enhanced activation of the right precuneus and left lingual gyrus in Alzheimer's patients are harder to interpret. The precuneus shows the highest resting metabolic rate of the human cerebral cortex (Gusnard and Raichle 2001), which reduces as Alzheimer's disease progresses (Buckner et al. 2005), possibly resulting in reduced modulation. Enhanced activation of the precuneus in our study could therefore be a consequence of disrupted metabolism. Studies in healthy participants have implicated the precuneus in (visuo-spatial) imagery (for review, see Cavanna and Trimble 2006) and propose an important role for the lingual gyrus in visual processing, since lesions of the lingual gyrus reduce dreaming and disable recognition of illusionary contours or faces (e.g., Girkin and Miller 2001). The enhanced activation of the precuneus and lingual gyrus observed in the Alzheimer's patients could be related to an attempted compensation for decreased vividness, as patients reported fewer event and perceptual details than healthy elderly during the autobiographical interview. This is, however, speculative. Recently, Kinkingnehun and colleagues (2008) found that the precuneus and lingual gyrus of "fast decliners" (mild Alzheimer's patients with a drop of nine MMSE points in three years) contained less grey matter at baseline compared to "slow decliners" (decrease of two MMSE points), ascribing a predictive value to this measure, since no clinical or neuropsychological differences were observed at baseline. Future studies can elucidate if enhanced activation is indicative of faster decline.

Since semantic memory is known to involve the temporal poles (Mummery et al. 2000), one might expect that a change in semantic processing, as expected in this study, would lead to activation differences in this area. In this study, both groups did activate the temporal poles when autobiographical and semantic statements were contrasted (**figure 3**), which is in accordance with sensitivity of the temporal poles to narrative stimuli and personal knowledge (Olson et al. 2007). We however, did not observe any differences between the healthy elderly and Alzheimer's patients in the temporal poles. This lack of activation difference between the groups is difficult to interpret. Probably, the demand on the temporal poles is equal to both groups.

One thing that remains unclear is the mechanism behind semantisation. This is especially interesting in the light of Alzheimer's disease, since it seems to work as a protective mechanism. If semantisation of AM is the result of rehearsal (because of telling the story repeatedly), than semantisation is more a by-product, leaving only the most salient memories available for remembering (see also Meeter and Murre 2004). This does not readily explain increased semantisation in Alzheimer's patients, since yet there are no indications that Alzheimer's patients are more reminiscent than healthy elderly.

In conclusion, the findings reported here show that Alzheimer's disease related MTL pathology is probably associated with semantisation of autobiographical memories in Alzheimer's patients, leading to increased semantic processing and presumably an increased dependence on the linking function of the vmPFC. These findings provide important insights in the consequences Alzheimer's disease has on the functionality of brain regions during AM retrieval and point at potential routes for early diagnosis.

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References

Addis, D.R., McIntosh, A.R., Moscovitch, M., Crawley, A.P. and McAndrews, M.P., 2004. Characterizing spatial and temporal features of autobiographical memory retrieval networks: a partial least squares approach. Neuroimage 23, 1460-71.

Addis, D.R., Moscovitch, M., Crawley, A.P. and McAndrews, M.P., 2004. Qualities of autobiographical memory modulate hippocampal activation during retrieval: preliminary findings of an fMRI study. Brain Cogn 54, 145-7.

Addis, D.R., Moscovitch, M., Crawley, A.P. and McAndrews, M.P., 2004. Recollective qualities modulate hippocampal activation during autobiographical memory retrieval. Hippocampus 14, 752-62.

Akirav, I. and Maroun, M., 2006. Ventromedial prefrontal cortex is obligatory for consolidation and reconsolidation of object recognition memory. Cereb Cortex 16, 1759-65.

Badre, D. and Wagner, A.D., 2005. Frontal Lobe Mechanisms that Resolve Proactive Interference. Cereb Cortex 15, 2003-2012.

Badre, D. and Wagner, A.D., 2007. Left ventrolateral prefrontal cortex and the cognitive control of memory. Neuropsychologia 45, 2883-901.

Blennow, K., de Leon, M.J. and Zetterberg, H., 2006. Alzheimer's disease. Lancet 368, 387-403.

Bontempi, B., Laurent-Demir, C., Destrade, C. and Jaffard, R., 1999. Time-dependent reorganization of brain circuitry underlying long-term memory storage. Nature 400, 671-5.

Bowie, C.R. and Harvey, P.D., 2006. Administration and interpretation of the Trail Making Test. Nat Protoc 1, 2277-81.

Braak, E., Griffing, K., Arai, K., Bohl, J., Bratzke, H. and Braak, H., 1999. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? Eur Arch Psychiatry Clin Neurosci 249 Suppl 3, 14-22.

Buckner, R.L., Snyder, A.Z., Shannon, B.J., LaRossa, G., Sachs, R., Fotenos, A.F., Sheline, Y.I., Klunk, W.E., Mathis, C.A., Morris, J.C. and Mintun, M.A., 2005. Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci 25, 7709-17.

Cabeza, R. and Nyberg, L., 2000. Imaging cognition II: An empirical review of 275 PET and fMRI studies. J Cogn Neurosci 12, 1-47.

Cabeza, R. and St Jacques, P., 2007. Functional neuroimaging of autobiographical memory. Trends Cogn Sci 11, 219-27.

Cavanna, A.E. and Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129, 564-83.

Chetelat, G., Desgranges, B., de la Sayette, V., Viader, F., Berkouk, K., Landeau, B., Lalevee, C., Le Doze, F., Dupuy, B., Hannequin, D., Baron, J.C. and Eustache, F., 2003. Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. Brain 126, 1955-67.

Conway, M.A., Pleydell-Pearce, C.W., Whitecross, S. and Sharpe, H., 2002. Brain imaging autobiographical memory. In: B.H. Ross (Ed.), The Psychology of Learning and Motivation. Vol. 41, Elsevier Science, pp. 229-264.

Curran, T., Schacter, D.L., Norman, K.A. and Galluccio, L., 1997. False recognition after a right frontal lobe infarction: memory for general and specific information. Neuropsychologia 35, 1035-49.

Daselaar, S.M., Rice, H.J., Greenberg, D.L., Cabeza, R., LaBar, K.S. and Rubin, D.C., 2008. The spatiotemporal dynamics of autobiographical memory: neural correlates of recall, emotional intensity, and reliving. Cereb Cortex 18, 217-29.

Dubois, B., Feldman, H.H., Jacova, C., Dekosky, S.T., Barberger-Gateau, P., Cummings, J., Delacourte, A., Galasko, D., Gauthier, S., Jicha, G., Meguro, K., O'Brien, J., Pasquier, F., Robert, P., Rossor, M., Salloway, S., Stern, Y., Visser, P.J. and Scheltens, P., 2007. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 6, 734-46.

Folstein, M.F., Folstein, S.E. and McHugh, P.R., 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12, 189-98.

Frankland, P.W. and Bontempi, B., 2005. The organization of recent and remote memories. Nat Rev Neurosci 6, 119-130.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-P., Frith, C.D. and Frackowiak, R.S.J., 1994. Statistical parametric maps in functional imaging: A general linear approach. Hum Brain Mapp 2, 189-210.

Gilboa, A., 2004. Autobiographical and episodic memory--one and the same? Evidence from prefrontal activation in neuroimaging studies. Neuropsychologia 42, 1336-49.

Gilboa, A., Alain, C., Stuss, D.T., Melo, B., Miller, S. and Moscovitch, M., 2006. Mechanisms of spontaneous confabulations: a strategic retrieval account. Brain 129, 1399-414.

Gilboa, A., Ramirez, J., Kohler, S., Westmacott, R., Black, S.E. and Moscovitch, M., 2005. Retrieval of autobiographical memory in Alzheimer's disease: relation to volumes of medial temporal lobe and other structures. Hippocampus 15, 535-50.

Girkin, C.A. and Miller, N.R., 2001. Central Disorders of Vision in Humans. Surv Ophthal 45, 379-405.

Grady, C.L., McIntosh, A.R., Beig, S., Keightley, M.L., Burian, H. and Black, S.E., 2003. Evidence from functional neuroimaging of a compensatory prefrontal network in Alzheimer's disease. J Neurosci 23, 986-93.

Grady, C.L., McIntosh, A.R. and Craik, F.I., 2005. Task-related activity in prefrontal cortex and its relation to recognition memory performance in young and old adults. Neuropsychologia 43, 1466-81.

Gusnard, D.A. and Raichle, M.E., 2001. Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci 2, 685-94.

Hagoort, P., Hald, L., Bastiaansen, M. and Petersson, K.M., 2004. Integration of word meaning and world knowledge in language comprehension. Science 304, 438-41.

Hayasaka, S. and Nichols, T.E., 2003. Validating cluster size inference: random field and permutation methods. Neuroimage 20, 2343-56.

Hulstaert, F., Blennow, K., Ivanoiu, A., Schoonderwaldt, H.C., Riemenschneider, M., De Deyn, P.P., Bancher, C., Cras, P., Wiltfang, J., Mehta, P.D., Iqbal, K., Pottel, H., Vanmechelen, E. and Vanderstichele, H., 1999. Improved discrimination of AD patients using beta-amyloid(1-42) and tau levels in CSF. Neurology 52, 1555-62.

Johnson, M.K. and Raye, C.L., 1998. False memories and confabulation. Trends Cogn Sci 2, 137-145.

Juengling, F.D. and Kassubek, J., 2003. Standardized calculation of brain parenchymal fraction: an approach to objective assessment of cerebral atrophy. AJNR Am J Neuroradiol 24, 1492-3; author reply 1493.

Killiany, R.J., Gomez-Isla, T., Moss, M., Kikinis, R., Sandor, T., Jolesz, F., Tanzi, R., Jones, K., Hyman, B.T. and Albert, M.S., 2000. Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Ann Neurol 47, 430-9.

Kinkingnehun, S., Sarazin, M., Lehericy, S., Guichart-Gomez, E., Hergueta, T. and Dubois, B., 2008. VBM anticipates the rate of progression of Alzheimer disease: a 3-year longitudinal study. Neurology 70, 2201-11.

Knoops, A.J., van der Graaf, Y., Appelman, A.P., Gerritsen, L., Mali, W.P. and Geerlings, M.I., 2009. Visual rating of the hippocampus in non-demented elders: Does it measure hippocampal atrophy or other indices of brain atrophy? The SMART-MR study. Hippocampus.

Kopelman, M.D., Wilson, B.A. and Baddeley, A.D., 1990. The autobiographical memory interview. Bury St. Edmonds: Thames Valley Test Company.

Levine, B., Svoboda, E., Hay, J.F., Winocur, G. and Moscovitch, M., 2002. Aging and autobiographical memory: dissociating episodic from semantic retrieval. Psychol Aging 17, 677-89.

Levine, B., Turner, G.R., Tisserand, D., Hevenor, S.J., Graham, S.J. and McIntosh, A.R., 2004. The functional neuroanatomy of episodic and semantic autobiographical remembering: a prospective functional MRI study. J Cogn Neurosci 16, 1633-46.

Lezak, M.D., Howieson, D.B. and Loring, D.W., 2004. Neuropsychological Assessment. 4 edn., Oxford University Press, New York.

Lynoe, N., Sandlund, M., Dahlqvist, G. and Jacobsson, L., 1991. Informed consent: study of quality of information given to participants in a clinical trial. BMJ 303, 610-3.

Maguire, E.A., 2001. Neuroimaging studies of autobiographical event memory. Philos Trans R Soc Lond B Biol Sci 356, 1441-51.

Maguire, E.A. and Mummery, C.J., 1999. Differential modulation of a common memory retrieval network revealed by positron emission tomography. Hippocampus 9, 54-61.

Meeter, M. and Murre, J.M., 2004. Consolidation of long-term memory: evidence and alternatives. Psychol Bull 130, 843-57.

Moscovitch, M., Nadel, L., Winocur, G., Gilboa, A. and Rosenbaum, R.S., 2006. The cognitive neuroscience of remote episodic, semantic and spatial memory. Curr Opin Neurobiol 16, 179-90.

Moscovitch, M. and Winocur, G., 2002. The frontal cortex and working with memory. In: D.T. Stuss and R. Knight (Eds.), Principles of frontal lobe function. Oxford University Press, New York, pp. 188-209.

Mummery, C.J., Patterson, K., Price, C.J., Ashburner, J., Frackowiak, R.S. and Hodges, J.R., 2000. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. Ann Neurol 47, 36-45.

Murphy, K.J., Troyer, A.K., Levine, B. and Moscovitch, M., 2008. Episodic, but not semantic, autobiographical memory is reduced in amnestic mild cognitive impairment. Neuropsychologia 46, 3116-23.

Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9, 97-113.

Olson, I.R., Plotzker, A. and Ezzyat, Y., 2007. The Enigmatic temporal pole: a review of findings on social and emotional processing. Brain 130, 1718-31.

Parkin, A.J., Bindschaedler, C., Harsent, L. and Metzler, C., 1996. Pathological false alarm rates following damage to the left frontal cortex. Brain Cogn 32, 14-27.

Patenaude, B., 2007. Bayesian Statistical Models of Shape and Appearance for Subcortical Brain Segmentation. University of Oxford.

Petersson, K.M., Elfgren, C. and Ingvar, M., 1999. Dynamic changes in the functional anatomy of the human brain during recall of abstract designs related to practice. Neuropsychologia 37, 567-587.

Petrides, M. and Pandya, D.N., 2002. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. Eur J Neurosci 16, 291-310.

Piefke, M., Weiss, P.H., Zilles, K., Markowitsch, H.J. and Fink, G.R., 2003. Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. Brain 126, 650-68.

Piolino, P., Desgranges, B., Benali, K. and Eustache, F., 2002. Episodic and semantic remote autobiographical memory in ageing. Memory 10, 239-57.

Reuter-Lorenz, P.A. and Lustig, C., 2005. Brain aging: reorganizing discoveries about the aging mind. Curr Opin Neurobiol 15, 245-51.

Schacter, D.L., Curran, T., Galluccio, L., Milberg, W.P. and Bates, J.F., 1996. False recognition and the right frontal lobe: a case study. Neuropsychologia 34, 793-808.

Scheltens, P., Leys, D., Barkhof, F., Huglo, D., Weinstein, H.C., Vermersch, P., Kuiper, M., Steinling, M., Wolters, E.C. and Valk, J., 1992. Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 55, 967-72.

Schwindt, G.C. and Black, S.E., 2009. Functional imaging studies of episodic memory in Alzheimer's disease: a quantitative meta-analysis. Neuroimage 45, 181-90.

Smith, S.M., Jenkinson, M., Woolrich, M.W., Beckmann, C.F., Behrens, T.E., Johansen-Berg, H., Bannister, P.R., De Luca, M., Drobnjak, I., Flitney, D.E., Niazy, R.K., Saunders, J., Vickers, J., Zhang, Y., De Stefano, N., Brady, J.M. and Matthews, P.M., 2004. Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23 Suppl 1, S208-19.

Squire, L.R., Ojemann, J.G., Miezin, F.M., Petersen, S.E., Videen, T.O. and Raichle, M.E., 1992. Activation of the hippocampus in normal humans: a functional anatomical study of memory. Proc Natl Acad Sci U S A 89, 1837-41.

Summerfield, J.J., Hassabis, D. and Maguire, E.A., 2009. Cortical midline involvement in autobiographical memory. Neuroimage 44, 1188-200.

Svoboda, E., McKinnon, M.C. and Levine, B., 2006. The functional neuroanatomy of autobiographical memory: a meta-analysis. Neuropsychologia 44, 2189-208.

Takashima, A., Petersson, K.M., Rutters, F., Tendolkar, I., Jensen, O., Zwarts, M.J., McNaughton, B.L. and Fernandez, G., 2006. Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Natl Acad Sci U S A 103, 756-61.

Takehara, K., Kawahara, S. and Kirino, Y., 2003. Time-dependent reorganization of the brain components underlying memory retention in trace eyeblink conditioning. J Neurosci 23, 9897-905.

Takehara-Nishiuchi, K. and McNaughton, B.L., 2008. Spontaneous Changes of Neocortical Code for Associative Memory During Consolidation. Science 322, 960-963.

Thompson-Schill, S.L., 2003. Neuroimaging studies of semantic memory: inferring "how" from "where". Neuropsychologia 41, 280-92.

Tulving, E., 1972. Episodic and semantic memory. In: E. Tulving and W. Donaldson (Eds.), Organization of Memory. Academic Press, New York, pp. 381–403.

Tulving, E., 2002. Episodic memory: from mind to brain. Annu Rev Psychol 53, 1-25.

Van der Elst, W., van Boxtel, M.P., van Breukelen, G.J. and Jolles, J., 2005. Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. J Int Neuropsychol Soc 11, 290-302.

van Kesteren, M.T., Fernandez, G., Norris, D.G. and Hermans, E.J., 2010. Persistent schema-dependent hippocampal-neocortical connectivity during memory encoding and postencoding rest in humans. Proc Natl Acad Sci U S A.

Verfaellie, M., Rapcsak, S.Z., Keane, M.M. and Alexander, M.P., 2004. Elevated false recognition in patients with frontal lobe damage is neither a general nor a unitary phenomenon. Neuropsychology 18, 94-103.

Wechsler, D., 1987. Manual for the Wechsler Memory Scale-Revised. Psychological Corporation, San Antonio, Texas.

Wechsler, D., 1997. Wechsler Adult Intelligence Scale. 3 edn., Psychological Corporation, San Antonio, Texas.

Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., Beckmann, C., Jenkinson, M. and Smith, S.M., 2009. Bayesian analysis of neuroimaging data in FSL. NeuroImage 45, S173-S186.

Yesavage, J.A., Brink, T.L., Rose, T.L., Lum, O., Huang, V., Adey, M. and Leirer, V.O., 1982. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 17, 37-49.

5

Chapter

Hippocampal decline in Alzheimer's disease affects ventromedial prefrontal cortex functioning

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Abstract

Medial temporal lobe (MTL) damage including the hippocampus is regarded the main cause of the declarative memory deficit emerging already early in Alzheimer's disease (AD). However, hippocampal decline might affect a more extended network, leading to impaired or enabling complementary processing in connected structures. Evidence is appearing that the ventromedial prefrontal cortex (vmPFC) has a similar role as the hippocampus in linking and integrating distributed representations during retrieval, at least when it comes to remote memories. In line with this, we observed in a previous AD study that the vmPFC can complement the hippocampus during autobiographical memory retrieval. To extend this finding to recent memory retrieval we explored, in a comprehensive study, the effects of AD on structural and functional integrity of the hippocampus and vmPFC in the memory network. We investigated 28 patients with early stage, probable AD and 25 healthy, matched controls by assessing 1) recognition memory performance; 2) brain morphology (voxel-based morphometry); 3) neural processing related to successful memory retrieval (event-related fMRI); and 4) functional hippocampal-vmPFC connectivity (resting-state fMRI). AD patients showed a typical memory deficit. Their grey matter reduction was pronounced in the MTL, but did not affect the vmPFC significantly. Compared to healthy controls, AD patients showed reduced hippocampal and vmPFC activity during successful memory retrieval and decreased functional connectivity between these structures during rest. These findings suggest that reduced hippocampal integrity causes a functional vmPFC impairment, potentially by disconnection. Therefore, the vmPFC appears unable to complement the hippocampus during retrieval of recently acquired information.

Introduction

The medial temporal lobe (MTL) with the hippocampus at its core, is well-known for its involvement in declarative memory (Cabeza and Nyberg 2000, Squire 1992) and it is thought to link and integrate distributed neocortical representations during encoding and retrieval (Marr 1970). In patients with Alzheimer's disease (AD), marked structural and functional decline of the MTL, in particular the hippocampus, is regarded as the main cause of its characteristic progressive declarative memory impairment (Backman et al. 1999, Blennow et al. 2006, Braak et al. 1999, Buckner et al. 2005, Chetelat and Baron 2003, Di et al. 2007, Killiany et al. 2000, Laakso et al. 1995). However, hippocampal decline might affect other structures within an associated network, resulting in either impaired or complementary processing in connected structures.

The MTL is closely linked to the (ventro)medial Prefrontal Cortex ([v]mPFC). Even though activation of the (v)mPFC is often observed in retrieval tasks (e.g. Dennis et al. 2008, Heun et al. 2004, Kircher et al. 2008, Summerfield et al. 2009), the precise role of the mPFC in memory is subject to discussion. Previous studies have attributed it to self-referential processing (Northoff et al. 2006), post-retrieval processing (Elliott et al. 2000, Moscovitch and Winocur 2002) and consolidation (van Kesteren et al. 2010). For instance, Takashima and colleagues (2006) found that hippocampal retrieval activity for pictures of spatial layouts reduces over the course of 90 days, while activity in the (v)mPFC increases. The authors related this observation to the concept of systems consolidation (Frankland and Bontempi 2005, Teyler and DiScenna 1986), which entails the reorganization of neural representations, for instance from the hippocampus to a neocortical region like the mPFC. In addition, the location of retrieval-related activation in the vmPFC might be task dependent: when probing memory for locations of face pictures, Takashima and colleagues (2007) found activation more anterior and superior compared to memory for pictures of spatial layouts (2006).

In rodents, neural firing in the mPFC becomes selective for acquired memories (associations) during consolidation (Takehara-Nishiuchi and McNaughton 2008), and sleep induces a memory-related functional connectivity between the hippocampus and the (v)mPFC (Gais et al. 2007). In addition, lesions of the (v)mPFC result in a selective retrieval deficit for remote but not recent memories (Akirav and Maroun 2006, Takehara et al. 2003), while lesions of the hippocampus can cause a retrieval deficit for recent memories (Eichenbaum 2000, Kim and Fanselow 1992, Scoville and

Milner 2000, Takehara et al. 2003). Functional connectivity between the vmPFC and the MTL is thought to support the integration of new memories (Tse et al. 2007), and enhancement of crosstalk between these areas can be compensatory, especially in the absence of a prior associative network, or schema (van Kesteren et al. 2010). These data indicate that the mPFC is involved in retrieval and consolidation, probably through interaction with the hippocampus. In other words, the mPFC might have a similar role as the hippocampus in linking and integrating distributed representations during retrieval, at least when it comes to remote memories.

In line with this notion, we observed a negative correlation between hippocampal size and activation of the vmPFC during autobiographical memory retrieval in AD patients in a previous study (Meulenbroek et al. 2010). This indicates that the vmPFC is able to complement the hippocampus during retrieval of remote memories. However, it remains unknown whether the vmPFC also complements the hippocampus during retrieval of information that has been encoded more recently, i.e. after the onset of the disease.

Therefore we examined, in a comprehensive study, the effects of AD on structural and functional integrity of the hippocampus and vmPFC in relation to recent memory retrieval. We investigated 28 patients with early stage, probable AD and 25 healthy, matched controls by assessing 1) recognition memory performance; 2) brain morphology (voxel-based morphometry, VBM); 3) neural processing related to successful recent memory retrieval (event-related functional Magnetic Resonance Imaging, fMRI) for 240 photographs of large-scale spatial layouts of natural landscapes; and 4) functional connectivity between the hippocampus and the vmPFC (resting-state fMRI).

Materials and methods

Participants

Twenty-five healthy older adults (Mean age [SD]= 70.8 [8.5]; years of education [SD]= 16.0 [3.4]; 17 male) and 28 patients (Mean age [SD]= 71.9 [6.9]; years of education [SD]= 15.3 [4.0]; 15 male) diagnosed with early stage, probable AD according to the research criteria from Dubois and colleagues (2007), who had a Clinical Dementia Rating (CDR) $\leq$ 1, participated in the fMRI experiment. Table 1 summarises the demographics and neuropsychological performance of participants. Exclusion criteria comprised: cerebrovascular disease (modified Hachinski score> 4), depression (Geriatric Depression Scale; GDS> 11), severe presbyacusis, claustrophobia, psycho-pharmacological drugs, low vision or metal implants. The local medical-ethics committee approved this study.

None of the healthy elderly reported subjective memory impairment or showed cognitive decline on the Mini-Mental State Examination (MMSE) or the second story of the subtest Logical Memory of the Wechsler Memory Scale–Revised (Wechsler 1987). All elderly participants were autonomous community dwellers: while mostly were retired, all were active in cultural pursuits, continuing education or with responsibilities in various associations. All were right-handed according to the Edinburgh handedness index (Oldfield 1971).

AD patients were recruited within three months from diagnosis from the Memory Clinic of the Alzheimer Centre at the Radboud University Nijmegen Medical Centre (N=26) and the Geriatrics department of the "Gelderse Vallei" hospital in Ede (N=2), the Netherlands. Diagnosis was supported by neuropsychological tests, assessing overall cognitive functioning with the MMSE (Folstein et al. 1975), working memory function using the Digit Span subtest of the Wechsler Adult Intelligence Test–Third Edition (WAIS-III) (Wechsler 1997), psychomotor speed and mental flexibility (as part of executive functioning) with the Trail Making Test (TMT) (Bowie and Harvey 2006), see table 1. The Rey Auditory Verbal Learning Test (RAVLT) functioned as an index of word-list learning, assessing immediate and delayed free recall and delayed recognition (Van der Elst et al. 2005). Test scores were classified as 'impaired' if they were more than 1.5 SD below the normative mean, corrected for age, education and sex (Lezak et al. 2004). The biomarker criterion for diagnosis of probable AD (Dubois et al. 2007) in this study was MTL atrophy determined by visual scoring (Scheltens et al. 1992), and/or abnormal cerebrospinal fluid (Hulstaert et al. 1999). All except one were right-handed according to the Edinburgh handedness index (Oldfield 1971).

Of the 25 healthy elderly, 9 were excluded for the memory paradigm: one because of low vision; two due to technical failure; one due to nausea; the other five were excluded from analysis, because performance was not significantly above chance level (N=2), there were less than 11 events per condition left after analysis of performance (N=3). None of the healthy elderly were excluded for the resting state or VBM analysis.

Of the 28 patients, 12 were excluded for the memory paradigm: one because of low vision; three MRI scans were aborted due to anxiety (N=2) or technical failure (N=2); the other seven were excluded from analysis, because performance was not significantly above chance level (N=6) or there were less than 11 events per condition left after performance analysis (N=1). During the resting state fMRI, 2 MRI scans were aborted due to anxiety. None of the patients were excluded for the VBM analysis.

Intake

At intake, informed consent according to the Declaration of Helsinki (Lynoe et al. 1991), and neuropsychological data were obtained. Patients were accompanied by proxy. After administration second story of the Logical Memory subtest of the WMS-R (Wechsler 1987), the MMSE (Folstein et al. 1975) and GDS (Yesavage et al. 1982), participants were comfortably seated at a desk in front of a laptop computer for a practice session with stimuli that were not used during the actual fMRI experiment. The experimental procedure of the practice session was identical to the one used during the fMRI experiment, except that the participants indicated their answers on the keypad of the laptop. More details are described below.

Afterwards, participants visited the MRI scanner suite, familiarising them with the experimental setup.

Memory paradigm fMRI: Stimulus material and experimental procedure

Participants returned for fMRI several weeks after intake.
During encoding (fMRI), participants were instructed to memorize 120 photographs of large-scale spatial layouts of natural landscapes with (N=60) or without buildings (N=60). Photographs were similar in terms of overall visual complexity, brightness, and contrast. They were presented for 800ms, separated by a fixation cross and randomly intermixed with 30 null events (fixation cross) of 2500ms each. Mean ISI was 2500ms (range 2000-3000ms). To monitor item processing, participants were asked to indicate by button press on a button box if the photograph contained a building or not.

The retrieval phase (fMRI) started within minutes after encoding. Participants now viewed 240 photographs (120 old, 120 new) and indicated by button press if the depicted scene was seen before or not, or if they were uncertain. Again the photographs were shown in random order for 800ms, separated by a fixation cross and randomly intermixed with 60 null events of 2500ms. Mean ISI was 4500ms (range

3500-5500ms). The stimuli were back-projected via an LCD-projector onto a translucent screen that participants viewed through a mirror on the head coil. Each photograph was presented in the centre of the screen, to minimize head movement. We used Presentation software (www.neurobs.com) to present stimuli and record button presses to be later analysed for hits, correct rejections, false alarms and misses.

Before going into the scanner, participants were extensively instructed and trained with stimuli (20 photographs) that were not used during the fMRI experiment.

Memory paradigm fMRI: Data acquisition

Whole head T2*-weighted EPI-BOLD fMRI data were acquired with Siemens Sonata (6 healthy elderly, 4 patients) and Avanto (10 healthy elderly, 12 patients) 1.5T MR scanners using an interleaved slice acquisition sequence (TR= 2.27s, TE= 30ms, 90° flip-angle, 33 axial slices, slice-matrix size= 64x64, slice thickness= 3.5mm, no gap, FOV= 224mm, isotropic voxel-size= 3.5x3.5x3.5mm3). High-resolution structural MR images were acquired with a T1-weighted MP-RAGE sequence (TR= 2.25s, TE= 3.93ms, 15° flip-angle, 176 sagittal slices, slice-matrix size=256x256, slice thickness= 1mm, voxel-size= 1x1x1mm3).

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Memory paradigm fMRI: MR Image preprocessing and statistical analysis

Image preprocessing and statistical analysis was done with SPM5 software (www.fil.ion.ucl.ac.uk). Functional EPI-BOLD images were realigned and subject-mean functional MR images were co-registered with the corresponding structural images using mutual information optimization. These were subsequently normalised (i.e., the normalisation transformations from the structural were applied to the functional images) and transformed into standardised MNI space defined by the MNI T1 template, and finally smoothed with an 8 mm Gaussian filter kernel (Hayasaka and Nichols 2003, Petersson et al. 1999). Preprocessing was inspected visually to verify if the co-registration and normalisation procedure worked properly and to check realignment parameters. The fMRI data were proportionally scaled to account for global effects and analyzed statistically using the general linear model and statistical parametric mapping (Friston et al. 1994). The linear model included explanatory variables (stick functions), convolved with the canonical hemodynamic response function, modelling hits, correct rejections, false alarms, misses and null events in an event-related fMRI design. The realignment parameters were added as regressors of no-interest. A temporal high-pass filter of 128s was applied to account for various low-frequency effects. Contrasts (each condition versus null events) for each participant were subjected to a second-level, random effects 2x4 ANCOVA, with Group as between-subject factor and Condition (hits, correct rejections, false alarms and misses) as within-subject factor. Scanner type (Avanto or Sonata), age of participant, d-prime and sex were included as covariates. Results of the random effects interaction analysis were thresholded initially at P=0.005 (uncorrected) and then small volume corrected (SVC) for the following a priori defined ROIs: (1) the hippocampus, as indicated by the Wake Forest University (WFU) Pick Atlas (Maldjian et al. 2003), and (2) the vmPFC, as indicated by a sphere with a 10mm radius around [MNI -2 32 -10], which is the same ROI as used by Takashima and colleagues (2006). This vmPFC ROI was chosen because our task was based on the same pictures as stimuli as in Takashima and colleagues.

Parameter estimates of significant clusters were extracted using Marsbar software (0.41, marsbar.sourceforge.net) for display purposes and post-hoc testing with SPSS 15.0 for Windows (Lead Technologies Inc. SPSS Inc., Chicago, Illinois, USA), to determine what drives the interaction effects.

Behavioural measures (performance, reaction times, hit rate/ false alarm rate, d-prime) were analysed with SPSS 15.0 for Windows (Lead Technologies Inc. SPSS Inc., Chicago, Illinois, USA). Reaction times of the two groups of participants were entered in an ANOVA with group as between-subjects factor (2 levels) and Condition as within-subjects factor (4 levels; hits, correct rejections, false alarms, misses). Alpha was set at 0.05.

Voxel Based Morphometry (VBM)

The structural MR images were normalized, bias-corrected, and segmented into grey matter, white matter, and cerebrospinal fluid with the VBM toolbox in SPM using priors (default settings). This method uses an optimized VBM protocol (Ashburner and Friston 2000, Good et al. 2001) as well as a model based on Hidden Markov Random Fields (HMRF) developed to increase signal-to-noise ratio (Cuadra et al. 2005). Diffeomorphic image registration was performed using the DARTEL toolbox in SPM (Ashburner 2007). Jacobian scaled ('modulated') images were calculated and subsequently transformed to MNI space using affine transformation. Finally, all data were smoothed with an 8 mm FWHM Gaussian smoothing kernel.

Grey matter and white matter images were subjected to a second-level, random effects two sample t-test, including scanner, age of participant and sex as covariates. Results of the t-test were thresholded initially at P=0.001 (uncorrected) and subsequently the cluster-size statistics were used as the test statistic at $P<0.05$ (FWE corrected). The grey matter results were masked for grey matter.

Resting State fMRI: experimental procedure and data acquisition

Using the same scanning parameters as during the memory paradigm, 300 volumes were acquired with Siemens Sonata (11 healthy elderly, 7 patients) and Avanto (14 healthy elderly, 19 patients) 1.5T MR scanners.

Participants were instructed to lie still with their eyes closed for ten minutes, not fall asleep and not to think of anything in particular (like counting), while lights in the scanner room were off.

Resting State fMRI: image preprocessing and statistical analysis

Image preprocessing was conducted in the same way as the data from the memory paradigm.

We defined the hippocampus in every participant using an automatic subneocortical segmentation tool implemented in FSL4.1 First v1.1 (Analysis Group, FMRIB, Oxford, UK) (Smith et al. 2004, Woolrich et al. 2009) on the normalized structural MRI. This procedure accounts for inter-individual differences in subneocortical anatomy, thus increasing the reliability and sensitivity of our analyses. The method is based on Bayesian statistical models of shape and appearance for seventeen sub and subneocortical structures from 317 manually labelled T1-weighted MR images (including brains from older persons and Alzheimer patients) (Patenaude 2007). Only boundary corrected data were used. Visual inspection of the segmented structures projected onto the T1-weighted MRI scans was done using MRIcroN Beta 7 (www.mricro.com/mricron), to check if the segmented structures align with the same structures on the T1.

Subsequently, the average time course of the segmented left hippocampus (which was the location of the interaction effect in the memory paradigm) was extracted from the unsmoothed (but normalized) images, using Marsbar software (0.41, http://marsbar.sourceforge.net).

Next, we entered this time course as a regressor of interest into a multiple regression analysis in SPM5. We also included several nuisance regressors to control for non-neuronal effects (regressor describing the time course of the ventricles, as defined by FSL4.1 First v1.1), for non-specific effects (regressor describing variations in global grey matter signal) and for motion effects (six movement regressors). All regressors were low-pass filtered before inclusion into the model (cut-off frequency at 0.1 Hz) to reduce cardiac and respiratory noise (Cordes et al. 2001, Fox and Raichle 2007). We also applied a temporal high-pass filter of 128 s to reduce low-frequency noise. Parameter estimates (beta values) for all regressors were obtained by maximum-likelihood estimation, modelling temporal autocorrelation as an AR(1) process. Thus, we tested for the contribution of the BOLD time series of the left hippocampus to the BOLD time series of all other voxels, while removing alternative sources of variance. We then compared the resulting connectivity maps across groups using a two-sample t-test at the second level. Scanner type, age of participant and sex were included as covariates (as was also done in the analysis of the memory paradigm), with additionally the scores from the Geriatric Depression Scale, because the AD patients had significantly higher scores than the healthy elderly.

Results of the t-test were thresholded initially at P=0.005 (uncorrected; same as used in the analysis of the memory paradigm), after which we focused our search on altered connectivity with the vmPFC (SVC on 10 mm sphere around MNI coordinates [-2 32 -10], same as used in the analysis of the memory paradigm).

Results

Behavioural Performance

On average, healthy elderly and AD patients performed the memory task above chance level (probability hit minus probability false alarm: healthy elderly 37% ± 12%, $t_{(15)}$=12.75, P<0.0001; AD patients 24% ± 9%, $t_{(15)}$=10.51, P<0.0001). Healthy elderly were better able to discriminate between old and new pictures than the AD patients (d-prime ± SD: healthy elderly 1.06 ± 0.34; AD patients 0.66 ± 0.26, $T_{(1,30)}$= 3.70, P<0.005).

No differences in reaction times were found, except that both groups became slower from hits, correct rejections, false alarms to misses (main effect of condition $F_{(1,28)}$= 10.07, P<0.001).

Functional MRI

To confirm that the hippocampus is involved in successful retrieval, we contrasted hits and correct rejections in healthy elderly. Activation was indeed observed in the hippocampus (left). In addition, activation of the vmPFC, as well as in the retrosplenial cortex, the left middle temporal gyrus and left inferior frontal gyrus was detected (**figure 1** and **table 2**).

Figure 1
Hits versus correct rejections contrast, in healthy elderly. (A) Activation of vmPFC and retrosplenial cortex at x = -8. (B) Activation of the hippocampus and middle temporal gyrus at y= -28. (A) and (B) are projected on the sagittal and coronal view of the mean normalised T1-image of 32 participants. Only significant clusters are shown ($P_{(FWE)}$ <.05).

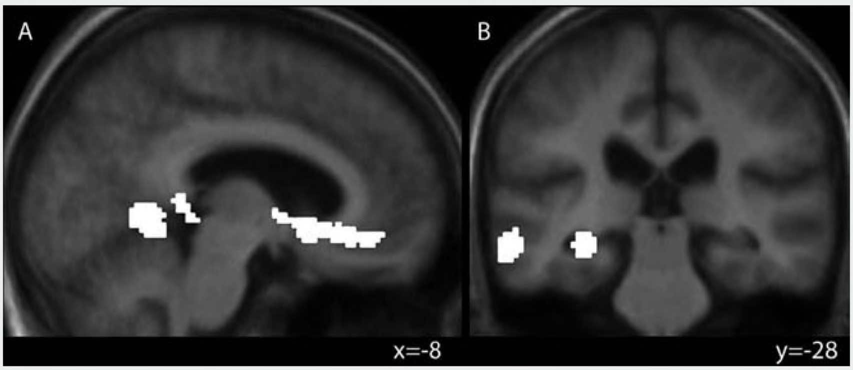


Table 1
Demographic data and behavioural results of the healthy elderly and AD patients.

	MEMORY PARADIGM						RESTING STATE					
Demographic characteristics												
	Healthy Elderly (N=16)			**Alzheimer's patients (N=16)**			**Healthy Elderly (N=25)**			**Alzheimer's patients (N=26)**		
	Mean	***SD***		***Mean***	***SD***		***Mean***	***SD***		***Mean***	***SD***	
Age	70.1	8.9		70.3	6.5		70.8	8.5		71.8	7.1	
Sex (male/total)			12/16			9/16			17/25			16/26
Education (years)	16.0	3.4		16.3	3.5		16.0	3.4		16.3	3.5	

Neuropsychological test performance for diagnosis												
	Healthy Elderly (N=16)			**Alzheimer's patients (N=16)**			**Healthy Elderly (N=25)**			**Alzheimer's patients (N=26)**		
Test	***Mean***	***SD***	***# impaired***	***Mean***	***SD***	***# impaired***	***Mean***	***SD***	***# impaired***	***Mean***	***SD***	***# impaired***
MMSE	*NA*			25.7	2.3	9	*NA*			24.6	3.0	18
Digit Span (WAIS-III)	*NA*					2	*NA*					5
Forward				8.6	2.5					8.7	2.2	
Backward				5.3	1.6					5.1	1.9	
RAVLT	*NA*						*NA*					
Immediate recall				23.9	6.1	12				23.8	7.0	19
Delayed recall				2.5	1.6	15				2.38	1.7	22
Delayed recognition				24.3	3.4	12				23.8	3.3	21
TMT	*NA*						*NA*					
Part A				60.3	48.9	3				67.2	42.2	5
Part B				148.1	77.3	4				164.1	96.1	8

Neuropsychological test performance during intake												
	Healthy Elderly (N=16)			Alzheimer's patients (N=16)			Healthy Elderly (N=25)			Alzheimer's patients (N=26)		
Test	*Mean*	*SD*	*# impaired*	*Mean*	*SD*	*# impaired*	*Mean*	*SD*	*# impaired*	*Mean*	*SD*	*# impaired*
MMSE	28.3	0.8	0	25.1***	2.8	10	28.1	1.1	0	24.3***	3.0	16
WMS-R Logical Memory II Delayed	12.5	3.9	0	4.6***	4.1	10	11.9	3.8	1	3.8***	3.9	17
GDS	3.0	3.5	0	3.8	2.2	0	2.5	3.1	0	4.5**	2.8	0

Performance during fMRI scan					
	Healthy Elderly (N=16)		Alzheimer's patients (N=16)		
	Mean	*SD*	*Mean*	*SD*	
Hit Rate	0.69	0.2	0.65	0.1	
False alarm Rate	0.31	0.1	0.41	0.1	P=0.05
d'	1.06		0.66**		
Hits	81	17	75	16	
Correct rejections	76	20	66	18	
False alarms	40	20	46	16	
Misses	36	19	40	15	
Reaction times (s):					
Hits	1.25	0.3	1.40	0.4	
Correct rejections	1.43	0.3	1.55	0.5	
False alarms	1.42	0.4	1.54	0.5	
Misses	1.6	0.4	1.6	0.6	

Note. MMSE = Mini-Mental State Examination; WAIS-III = Wechsler Adult Intelligence Scale – Third Edition; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test; WMS-R = Wechsler Memory Scale – Revised; GDS = Geriatric Depression Scale; *** P<.001; *P<.05. "# impaired" was based on available normative data for the memory tests.

Table 2

Functional MRI and VBM results.

MEMORY

Contrast	Region	Brodmann Area	Size	Z	Local maxima		
					x	y	z
Healthy elderly Hits > Correct rejections	Middle temporal gyrus (l)	20	430	5.02	-60	-42	-12
	Lingual gyrus/Hippocampus (l)	19/30	354	4.53	-8	-52	-2
	Superior occipital gyrus (l)	19/39	351	4.53	-40	-80	34
	vmPFC extending to caudate (l)	24/25	344	4.50	-6	16	-6
	Hippocampus (l)		179	4.36	-32	-28	-12
	Inferior frontal gyrus (l)	47	181	4.05	-30	26	-10
Correct rejections > Hits	*No significant clusters*						
Patients Hits <> Correct rejections	*No significant clusters*						
Interaction Healthy elderly> Patients & Hits> Correct rejections					x	y	z
	SVC hippocampus		8	3.07	-32	-28	-12
	SVC vmPFC		29	3.30	-8	26	-6

VBM (GRAY MATTER)

Contrast	Region	Brodmann Area	Size	Z	Local maxima		
					x	y	z
Healthy elderly > Patients	(Para)hippocampus (l) to amydala; Hippocampal tail (l); Precuneus and Retrosplenial cortex to middle occipital (l+r)	7/18/28/31/ 34/36/38	71666	5.21	-20	-10	-34
	(para)hippocampus to amygdala (r)	28	7198	5.20	20	-11	-33

Healthy elderly > Patients	Inferior temporal gyrus (r)	20	2922	4.42	37	-11	-47
	Inferior temporal gyrus (l)	20	1466	4.17	-66	-23	-23
	Middle temporal gyrus (r)	21	1910	4.09	52	-26	-5
	Insula (l)	13	1895	3.98	-44	-6	-10
Patients > Healthy elderly	*No significant clusters*						

VBM (WHITE MATTER)

Contrast	**Region**	**Size**	**Z**	**Local maxima**		
				x	**y**	**z**
Healthy elderly > Patients	Optic radiation (l)	4661	4.50	-29	-45	11
	Paraterminal gyrus (r) (anterior to optic chiasm)	1046	4.43	5	17	-25
	Uncus (l)	1537	4.21	-24	-20	-26
	Optic radiation (r)	1340	4.06	26	-45	14
Patients > Healthy elderly	*No significant clusters*					

Note. IFG= Inferior Frontal Gyrus; vmPFC= ventromedial Prefrontal Cortex; (l)= left; (r)= right; Local maxima are in MNI space.

Next we investigated the interaction between the task conditions (hits and correct rejections) and the participant groups (healthy elderly and AD patients). Two interactions effects were observed: in the (left) hippocampus ($P_{(SVC)}$<0.05) and vmPFC ($P_{(SVC)}$<0.05) (**figure 2**). Analysis of the simple effects revealed these interaction effects were driven by the increased activation for hits versus correct rejections in these areas in healthy elderly.

Figure 2
Interaction effects of healthy elderly versus AD patients, in the hits versus correct rejections contrast: (A) Hippocampus: peak [-32 -28 -12] (ROI WFU Pick atlas); (B) vmPFC: peak [-8 26 -6] (ROI 10 mm sphere around [-2 32 -10]). Extracted parameter estimates (in arbitrary units; A.U.) of the whole clusters are shown alongside the images, for display purposes. (A) and (B) are projected on the coronal and sagittal view of the mean normalised T1-image of 32 participants. Only significant clusters are shown ($P_{(SVC)}$ <.05).

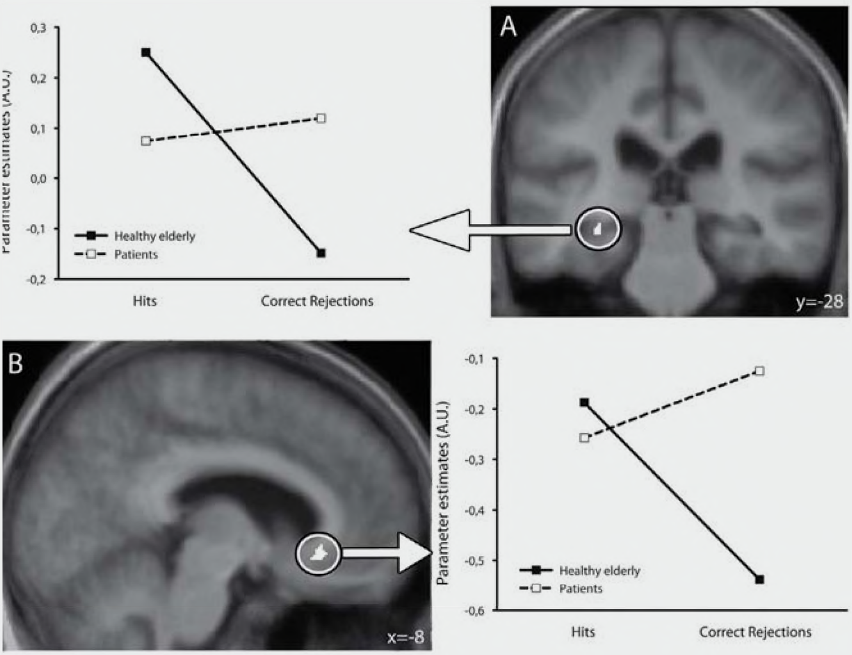
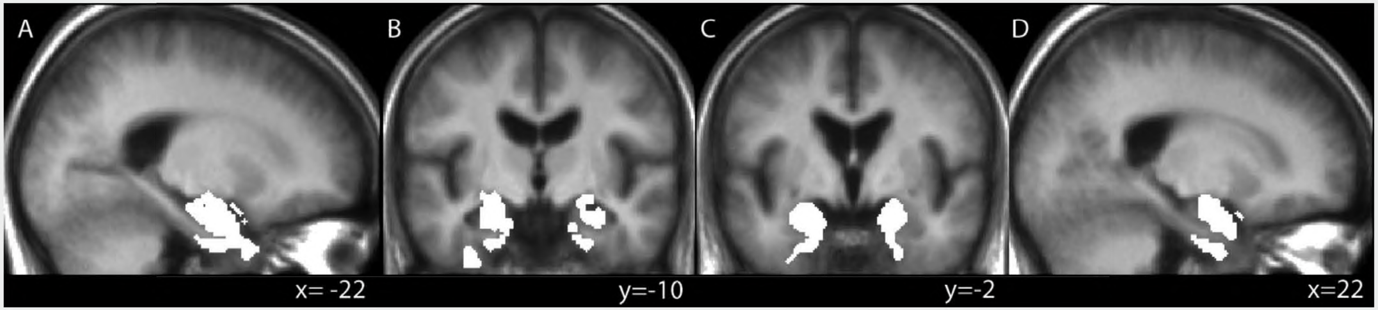


Figure 3
VBM results, showing the main grey matter differences between healthy elderly and AD patients in the MTL. Results are projected on the coronal view of the mean normalised T1-image of 32 participants. Only significant clusters are shown (P(FWE) <.05).



VBM

The VBM analysis showed extensive grey-matter atrophy in AD patients in the (para) hippocampal region and amygdala, the superior, medial and inferior temporal gyrus, the occipital and retrosplenial cortex, when compared to healthy elderly. No significant grey matter differences were observed in the vmPFC (**figure 3** and **table 2**).

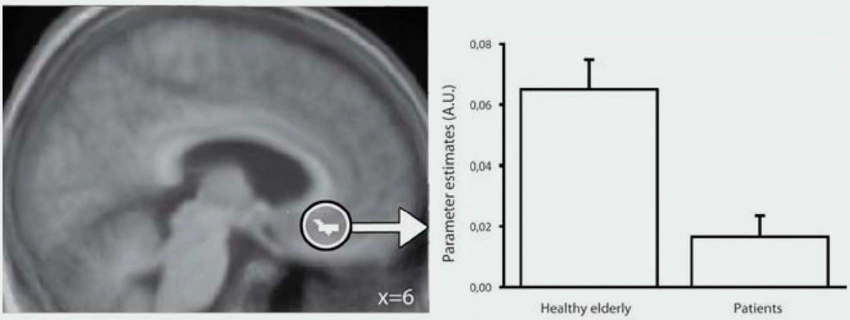
White-matter atrophy was observed in AD patients in the optic radiation (left and right), the left uncus and paraterminal gyrus (data not shown).

Resting State

AD patients displayed decreased functional connectivity of the left hippocampus with the vmPFC (P(SVC)<0.05; same ROI as in the recognition paradigm) compared to healthy elderly (**figure 4**).

Figure 4

Functional connectivity of the left hippocampus with the vmPFC (ROI 10 mm sphere around [-2 32 -10]) during rest. Extracted parameter estimates (in arbitrary units; A.U.) of the whole cluster are shown alongside the image, for display purposes. The cluster is projected on the sagittal view of the mean normalised T1-image of 32 participants. Only significant clusters are shown ($P_{(SVC)}$ <.05).



Discussion

The results of our study suggest that reduced hippocampal integrity in AD results in a functional vmPFC impairment, potentially by disconnection of these structures. Therefore, the vmPFC appears unable to complement the hippocampus during retrieval of recently acquired information.

By employing a retrieval task for photographs of large-scale spatial layouts of natural landscapes in AD patients and healthy elderly, we found that AD patients had a decreased capacity to discriminate between old and new pictures. Grey-matter reduction in AD patients was pronounced in the medial temporal lobe, but did not significantly affect the vmPFC region at issue. Compared to healthy elderly, AD patients showed reduced hippocampal and vmPFC activity during successful memory retrieval. In addition, functional connectivity between these structures during rest was reduced in the AD patients.

The indication of the results in this study that the vmPFC is unable to complement the hippocampus extends our previous study (Meulenbroek et al. 2010), in which we report that activation of the vmPFC during autobiographical memory retrieval (compared to semantic retrieval) increases with decreasing hippocampal size, indicating complementary processing by the vmPFC. The main difference between the two memory paradigms is that the present study probed recent memories, while the previous study probed remote or well-consolidated memories typically acquired before disease onset. This dissociation suggests and supports the hypothesis that interaction between the hippocampus and mPFC is beneficial to acquisition and consolidation of new information (van Kesteren et al. 2010) and that this interaction is no longer crucial during retrieval of consolidated memories (Meulenbroek et al. 2010, Takashima et al. 2006).

Grey-matter reduction in AD patients was pronounced in the MTL (entorhinal/ (para) hippocampal cortex), which is in line with previous reports (Buckner et al. 2005, Chetelat and Baron 2003). This structural change was accompanied by decreased activation in the hippocampus during the retrieval task in the same patients. This corroborates earlier studies (Dickerson and Sperling 2008). Since the grey-matter reduction did not affect the vmPFC significantly, the decreased activation observed there has no apparent structural analogue. However, AD patients did display decreased functional connectivity between these two regions during rest. All these findings together, obtained in one sample of participants, support the idea that the observed functional decrease of the vmPFC is related to the AD-specific structural and functional decline of the MTL, leading to disconnection (Bird and Burgess 2008, Bokde et al. 2009, Stam et al. 2007, Stephen et al. 2010, Villain et al. 2008).

The vmPFC and MTL are intricately connected through the uncinate fasciculus and the cingulum (Markowitsch 1995, Petrides and Pandya 2002). Hence, one might expect that functional disconnection between the vmPFC and MTL is reflected by a decrease in the white matter that connects these two areas. However, this was not the case in the present study, which may indicate that these early differences could not (yet) be detected with VBM. In contrast, white-matter degradation was observed in the left uncus, which is the anterior part of the parahippocampal gyrus that the uncinate fasciculus projects to (Ebeling and Cramon 1992). This supports the disconnection hypothesis.

The AD patients had a decreased capacity to discriminate between old and new pictures, which is in line with the AD-related memory problems (Balota et al. 1999, Morris 1996, Schacter et al. 1998, Small et al. 1997) and is reflected by their slightly increased false alarm rate (P=0.05). The decreased capacity to discriminate between old and new pictures in this study is also reflected by the need to exclude 6 patients due to chance-level performance. These patients had equally distributed amounts of hits, correct rejections, false alarms and misses, indicating guessing.

In conclusion, the findings reported here show that AD-related memory-retrieval impairment is associated with decreased functionality of the vmPFC, which is probably due to structural and functional damage of the hippocampus leading to disconnection. As a result, the vmPFC is unable to complement the hippocampus during retrieval of recently acquired information. These findings provide important insights in the consequences AD has on the functionality of brain networks and point at potential routes for early diagnosis.

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References

Akirav I, Maroun M. Ventromedial prefrontal cortex is obligatory for consolidation and reconsolidation of object recognition memory. Cereb Cortex 2006; 16: 1759-65.

Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007; 38: 95-113.

Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage 2000; 11: 805-821.

Backman L, Andersson JL, Nyberg L, Winblad B, Nordberg A, Almkvist O. Brain regions associated with episodic retrieval in normal aging and Alzheimer's disease. Neurology 1999; 52: 1861-1870.

Balota DA, Cortese MJ, Duchek JM *et al.* Veridical and false memories in healthy older adults and in dementia of the Alzheimer's type. Cognitive Neuropsychology 1999; 16: 361-384.

Bird CM, Burgess N. The hippocampus and memory: insights from spatial processing. Nat Rev Neurosci 2008; 9: 182-194.

Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet 2006; 368: 387-403.

Bokde AL, Ewers M, Hampel H. Assessing neuronal networks: understanding Alzheimer's disease. Prog Neurobiol 2009; 89: 125-133.

Bowie CR, Harvey PD. Administration and interpretation of the Trail Making Test. Nat Protoc 2006; 1: 2277-81.

Braak E, Griffing K, Arai K, Bohl J, Bratzke H, Braak H. Neuropathology of Alzheimer's disease: what is new since A. Alzheimer? Eur Arch Psychiatry Clin Neurosci 1999; 249 Suppl 3: 14-22.

Buckner RL, Snyder AZ, Shannon BJ *et al.* Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci 2005; 25: 7709-17.

Cabeza R, Nyberg L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. J Cogn Neurosci 2000; 12: 1-47.

Chetelat G, Baron JC. Early diagnosis of Alzheimer's disease: contribution of structural neuroimaging. Neuroimage 2003; 18: 525-541.

Cordes D, Haughton VM, Arfanakis K *et al.* Frequencies contributing to functional connectivity in the cerebral cortex in "resting-state" data. AJNR Am J Neuroradiol 2001; 22: 1326-1333.

Cuadra MB, Cammoun L, Butz T, Cuisenaire O, Thiran JP. Comparison and validation of tissue modelization and statistical classification methods in T1-weighted MR brain images. IEEE Trans Med Imaging 2005; 24: 1548-1565.

Dennis NA, Kim H, Cabeza R. Age-related differences in brain activity during true and false memory retrieval. J Cogn Neurosci 2008; 20: 1390-1402.

Di PM, Macaluso E, Carlesimo GA *et al.* Episodic memory impairment in patients with Alzheimer's disease is correlated with entorhinal cortex atrophy. A voxel-based morphometry study. J Neurol 2007; 254: 774-781.

Dickerson BC, Sperling RA. Functional abnormalities of the medial temporal lobe memory system in mild cognitive impairment and Alzheimer's disease: insights from functional MRI studies. Neuropsychologia 2008; 46: 1624-1635.

Dubois B, Feldman HH, Jacova C *et al.* Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007; 6: 734-46.

Ebeling U, Cramon D. Topography of the uncinate fascicle and adjacent temporal fiber tracts. Acta Neurochirurgica 1992; 115: 143-148.

Eichenbaum H. A cortical-hippocampal system for declarative memory. Nat Rev Neurosci 2000; 1: 41-50.

Elliott R, Dolan RJ, Frith CD. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. Cereb Cortex 2000; 10: 308-317.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-98.

Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007; 8: 700-711.

Frankland PW, Bontempi B. The organization of recent and remote memories. Nat Rev Neurosci 2005; 6: 119-130.

Friston KJ, Holmes AP, Worsley KJ, Poline J-P, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: A general linear approach. Hum Brain Mapp 1994; 2: 189-210.

Gais S, Albouy G, Boly M *et al.* Sleep transforms the cerebral trace of declarative memories. Proc Natl Acad Sci U S A 2007; 104: 18778-18783.

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001; 14: 21-36.

Hachinski VC, Iliff LD, Zilhka E *et al.* Cerebral blood flow in dementia. Arch Neurol 1975; 32: 632-637.

Hayasaka S, Nichols TE. Validating cluster size inference: random field and permutation methods. NeuroImage 2003; 20: 2343-56.

Heun R, Jessen F, Klose U, Erb M, Granath DO, Grodd W. Response-related fMRI of veridical and false recognition of words. Eur Psychiatry 2004; 19: 42-52.

Hulstaert F, Blennow K, Ivanoiu A *et al.* Improved discrimination of AD patients using beta-amyloid(1-42) and tau levels in CSF. Neurology 1999; 52: 1555-62.

Killiany RJ, Gomez-Isla T, Moss M *et al.* Use of structural magnetic resonance imaging to predict who will get Alzheimer's disease. Ann Neurol 2000; 47: 430-9.

Kim JJ, Fanselow MS. Modality-specific retrograde amnesia of fear. Science 1992; 256: 675-677.

Kircher T, Weis S, Leube D *et al.* Anterior hippocampus orchestrates successful encoding and retrieval of non-relational memory: an event-related fMRI study. Eur Arch Psychiatry Clin Neurosci 2008; 258: 363-372.

Laakso MP, Soininen H, Partanen K *et al.* Volumes of hippocampus, amygdala and frontal lobes in the MRI-based diagnosis of early Alzheimer's disease: correlation with memory functions. J Neural Transm Park Dis Dement Sect 1995; 9: 73-86.

Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. New York: Oxford University Press; 2004.

Lynoe N, Sandlund M, Dahlqvist G, Jacobsson L. Informed consent: study of quality of information given to participants in a clinical trial. BMJ 1991; 303: 610-3.

Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. Neuroimage 2003; 19: 1233-1239.

Markowitsch HJ. Which brain regions are critically involved in the retrieval of old episodic memory? Brain Res Brain Res Rev 1995; 21: 117-127.

Marr D. A theory for cerebral neocortex. Proc R Soc Lond B Biol Sci 1970; 176: 161-234.

Meulenbroek O, Rijpkema M, Kessels RP, Rikkert MG, Fernandez G. Autobiographical memory retrieval in patients with Alzheimer's disease. Neuroimage 2010.

Morris RG. The cognitive neuropsychology of Alzheimertype dementia. Oxford: Oxford University Press; 1996.

Moscovitch M, Winocur G. The frontal cortex and working with memory. In: Stuss DT, Knight R, editors. Principles of frontal lobe function. New York: Oxford University Press; 2002. p. 188-209.

Northoff G, Heinzel A, de GM, Bermpohl F, Dobrowolny H, Panksepp J. Self-referential processing in our brain--a meta-analysis of imaging studies on the self. Neuroimage 2006; 31: 440-457.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971; 9: 97-113.

Patenaude B. Bayesian Statistical Models of Shape and Appearance for Subcortical Brain Segmentation. University of Oxford; 2007.

Petersson KM, Elfgren C, Ingvar M. Dynamic changes in the functional anatomy of the human brain during recall of abstract designs related to practice. Neuropsychologia 1999; 37: 567-587.

Petrides M, Pandya DN. Comparative cytoarchitectonic analysis of the human and the macaque ventrolateral prefrontal cortex and corticocortical connection patterns in the monkey. Eur J Neurosci 2002; 16: 291-310.

Schacter DL, Norman KA, Koutstaal W. The cognitive neuroscience of constructive memory. Annu Rev Psychol 1998; 49: 289-318.

Scheltens P, Leys D, Barkhof F *et al.* Atrophy of medial temporal lobes on MRI in «probable» Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 1992; 55: 967-72.

Scoville WB, Milner B. Loss of Recent Memory After Bilateral Hippocampal Lesions. J Neuropsychiatry Clin Neurosci 2000; 12: 103-10a.

Small BJ, Herlitz A, Fratiglioni L, Almkvist O, Backman L. Cognitive predictors of incident Alzheimer's disease: a prospective longitudinal study. Neuropsychology 1997; 11: 413-420.

Smith SM, Jenkinson M, Woolrich MW *et al.* Advances in functional and structural MR image analysis and implementation as FSL. NeuroImage 2004; 23 Suppl 1: 208-19.

Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 1992; 99: 195-231.

Stam CJ, Jones BF, Nolte G, Breakspear M, Scheltens P. Small-world networks and functional connectivity in Alzheimer's disease. Cereb Cortex 2007; 17: 92-99.

Stephen JM, Montano R, Donahue CH *et al.* Somatosensory responses in normal aging, mild cognitive impairment, and Alzheimer's disease. J Neural Transm 2010; 117: 217-225.

Summerfield JJ, Hassabis D, Maguire EA. Cortical midline involvement in autobiographical memory. NeuroImage 2009; 44: 1188-200.

Takashima A, Nieuwenhuis IL, Rijpkema M, Petersson KM, Jensen O, Fernandez G. Memory trace stabilization leads to large-scale changes in the retrieval network: a functional MRI study on associative memory. Learn Mem 2007; 14: 472-479.

Takashima A, Petersson KM, Rutters F *et al.* Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Natl Acad Sci U S A 2006; 103: 756-61.

Takehara K, Kawahara S, Kirino Y. Time-dependent reorganization of the brain components underlying memory retention in trace eyeblink conditioning. J Neurosci 2003; 23: 9897-905.

Takehara-Nishiuchi K, McNaughton BL. Spontaneous Changes of Neocortical Code for Associative Memory During Consolidation. Science 2008; 322: 960-963.

Teyler TJ, DiScenna P. The hippocampal memory indexing theory. Behav Neurosci 1986; 100: 147-154.

Tse D, Langston RF, Kakeyama M *et al.* Schemas and memory consolidation. Science 2007; 316: 76-82.

Van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. J Int Neuropsychol Soc 2005; 11: 290-302.

van Kesteren MT, Fernandez G, Norris DG, Hermans EJ. Persistent schema-dependent hippocampal-neocortical connectivity during memory encoding and postencoding rest in humans. Proc Natl Acad Sci U S A 2010; 107: 7550-7555.

Villain N, Desgranges B, Viader F *et al.* Relationships between hippocampal atrophy, white matter disruption, and gray matter hypometabolism in Alzheimer's disease. J Neurosci 2008; 28: 6174-6181.

Wechsler D. Manual for the Wechsler Memory Scale-Revised. San Antonio, Texas: Psychological Corporation; 1987.

Wechsler D. Wechsler Adult Intelligence Scale. San Antonio, Texas: Psychological Corporation; 1997.

Woolrich MW, Jbabdi S, Patenaude B *et al.* Bayesian analysis of neuroimaging data in FSL. NeuroImage 2009; 45: S173-S186.

Yesavage JA, Brink TL, Rose TL *et al.* Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982; 17: 37-49.

6

Chapter

Summary and Discussion

The studies reported in this thesis aimed to provide more insight into episodic memory processes that become impaired in aging and (early stage) Alzheimer's disease (AD). In this final chapter I will summarize and discuss the main findings in relation to current theories on episodic memory, focusing on the main structures involved: the medial temporal lobe (MTL), the prefrontal cortex (PFC) and the retrosplenial cortex (RSC), and on the role of compensation in healthy aging and AD. Furthermore, I will provide suggestions for future research.

Summary

In chapter 2 the neural correlates of spatial memory encoding and retrieval in aging were investigated, in a task using routes through virtual houses. Elderly were slightly impaired at route recognition, compared to the young participants. During encoding, elderly displayed decreased activation of the dorsal and ventral visual processing stream, and increased activation of the perisylvian region and ventromedial prefrontal cortex (vmPFC). These findings were interpreted as an age-related navigational memory deficit caused by less effective route encoding based on reduced posterior fusiform/parahippocampal and parietal functionality. This was combined with diminished inhibition of perisylvian and vmPFC, which was attributed to less effective suppression of task irrelevant information. During recognition, elderly displayed decreased activation of the retrosplenial cortex (RSC), while activation in the parahippocampal gyrus and medial part of the RSC was increased, which was interpreted as a diminished familiarity signal during route recognition in the anterior parahippocampal region.

Chapter 3 studied the effect of environmental support during encoding on retrieval of object place associations in aging. Rich environmental support was only systematically used by the young participants, who placed objects next to each other. During fMRI, rich environmental support during encoding led to increased activation of the basal ganglia, thalamus, medial temporal gyrus, fusiform gyrus and right medial temporal lobe (MTL) in the elderly participants compared to the young. These differences were interpreted as additional recruitment of the episodic memory system by the elderly, in addition to a fronto-striatal network, which indicated that the elderly probably tried to use stimulus-response associations to solve the task.

In chapter 4, autobiographical memory retrieval was compared with semantic memory retrieval in healthy elderly and AD patients. Results indicated increased semantisation of autobiographical memories in AD patients compared to healthy elderly. During fMRI, AD patients showed enhanced activity in the left inferior frontal gyrus (LIFG), vmPFC, right precuneus and left lingual gyrus. Activation of LIFG and vmPFC was significantly negatively correlated with hippocampal volume in patients only, which was interpreted as an attempt to compensate for hippocampal degradation.

Chapter 5 further explored the effects of AD on structural and functional integrity of the hippocampus and vmPFC in the memory network, using multiple measures: (1) recognition memory performance; (2) brain morphology (voxel-based morphometry); (3) neural processing related to successful memory retrieval (event-related fMRI); and (4) functional connectivity between the hippocampus and vmPFC (resting-state fMRI). AD patients showed poorer memory performance and gray matter reductions were pronounced in the medial temporal lobe, but structural decline did not affect the vmPFC significantly. Compared to healthy controls, AD patients showed reduced hippocampal and vmPFC activity during successful memory retrieval and functional connectivity between these structures. Therefore, the functional decline of the vmPFC was attributed to reduced structural and functional integrity of the hippocampus, possibly by disconnection. As a consequence, the vmPFC could not complement the hippocampus during retrieval of recently acquired information.

Below is an overview of the main findings (from fMRI) of this thesis and their interpretations (table 1), as reported in the different chapters.

In all studies reported in this thesis, behavioural performance of the study group was impaired compared to the control group. The magnitude of the behavioural differences corresponded with task difficulty: recognition paradigms (chapter 2 and 5) are considered to be easier than cued recall (chapter 3 and 4) (for review, see Gabrieli 1998), because these tasks require less self-initiated (strategic) processing. In general it can therefore be concluded that the episodic memory processes investigated in this thesis are all affected: either by aging (chapters 2 and 3) or AD (chapters 4 and 5).

Since interest in this thesis was mainly on differences in brain processing that do not simply reflect differences in performance, behavioural performance was added to the model as a regressor of no interest during the analyses (except in chapter 2, in which the performance differences were only subtle), to facilitate interpretation of the activation differences.

Table 1
Overview of main findings from fMRI, as reported in this thesis.

	Chapter	Groups	Brain Region	Effect	Interpretation
2	Route encoding	Healthy Elderly > Young	Dorsal/ventral stream	Decrease	Impairment
			Perisylvian/ vmPFC	Increase	Impairment: Inhibition failure
	Route recognition		Parahippocampal gyrus		Impairment (chapter) Compensation (discussion)
			RSC		Compensation
3	Object-location cued recall	Healthy Elderly > Young	Basal ganglia/ Thalamus MTG/ fusiform gyrus right MTL	Increase	Different strategy
4	Autobiographical memory retrieval	AD patients > Healthy Elderly	LIFG/ vmPFC	Increase	Attempted compensation: Negative correlation with hippocampal volume
			Precuneus/ Lingual gyrus		Impairment
5	Recognition of pictures	AD patients > Healthy Elderly	vmPFC/ Hippocampus	Decrease	Impairment: Reduced functional connectivity

As can also be seen from table 1, activation differences described throughout this thesis were observed in the main structures that support episodic memory: the medial temporal lobe (MTL), the prefrontal cortex (PFC) and the retrosplenial cortex (RSC):

The medial temporal lobe (MTL)

In chapter 2 and 3, increased activation in the right parahippocampal cortex was observed in healthy elderly compared to young during retrieval. In chapter 3, this difference was observed during cued recall of object-location associations that were encoded while rich environmental support was provided. This encoding situation was very similar to the route encoding situation in chapter 2, where environmental support was provided by the placement of furniture near corners (decision points). In chapter 2 the increased right parahippocampal activation was tentatively attributed to a missing familiarity signal in the elderly. Upon reconsideration, it is plausible however that differences in the parahippocampal cortex are attributable to spatial processing (Kessels et al. 2001), since a large body of research has since then implicated the parahippocampal cortex in representation of allocentric spatial relationships between landmarks (Moscovitch et al. 2005, Moscovitch et al. 2006) or objects (Burgess et al. 2001, Byrne et al. 2007). These representations are then passed to the hippocampus for memory indexing or binding (Moscovitch et al. 2006).

Other studies have observed decreased right parahippocampal activation in elderly, but then during encoding of virtual environments (Moffat et al. 2006), and this activation correlated positively with performance. Increased activation of the parahippocampal cortex in elderly is only observed during retrieval (of -spatial components of- autobiographical memories) (Cabeza et al. 2004, Maguire and Frith 2003). Van der Veen and colleagues (2006) observed that increased activation of the right parahippocampal gyrus in healthy elderly correlated positively with memory performance. Therefore, the observed increased activation in the right parahippocampal cortex of elderly is likely to be related to compensation.

In the studies involving AD patients (chapter 4 and 5) hippocampal atrophy was observed, which is in line with AD pathology (Blennow et al. 2006, Braak and Braak 1991). Only in chapter 5 decreased hippocampal activation in the patients was observed, corresponding to AD-related hippocampal dysfunction (Backman et al. 1999, Dickerson et al. 2005, Grady et al. 1994, Petrella et al. 2007, Sperling et al. 2003). The lack of activation difference in the hippocampus in chapter 4 is hard to interpret, but the characteristics of the two memory tasks may give some indications:

In chapter 4 the retrieval of (the episodic aspects of) autobiographical memories was investigated. These are memories that were (almost all) acquired before disease onset, and thus are well-consolidated. The retrieval of recently learned photographs, which was investigated in chapter 5, regarded newly acquired memories, and therefore these can be considered to be not well-consolidated.

Two hypotheses may follow from these results, which already have substantial support in literature:

1) The hippocampus is involved in retrieval of newly acquired episodic memories. Dysfunction of the hippocampus leads to impaired retrieval when memories are "new". This is in line with previous research, like lesion studies (Eichenbaum 2000, Kim and Fanselow 1992, Scoville and Milner 2000), and retrieval activation studies (Squire et al. 2004).
2) Episodic memories that are acquired before onset of AD, remain preserved at least in the early stage of the disease. Even though the hippocampus is already compromised, its activation is either not crucial for the task at hand, and/or patients can compensate (for discussion, see Moscovitch et al. 2006).

All together, it can be concluded that in aging, the MTL remains relatively preserved (Insausti et al. 1998, Raz 2005) and can therefore exhibit compensatory processing, for instance in spatial memory. In AD however, the extent of MTL damage prohibits compensatory processing in the MTL. Instead, these processes take place elsewhere in the brain:
In chapter 4 it was observed that patients tried to compensate for hippocampal atrophy by recruiting the vmPFC.

The prefrontal cortex (PFC)

Activation differences in the PFC were observed in healthy elderly (chapter 2) and AD patients (chapters 4 and 5). In healthy elderly, the activation was increased (chapter 2), while in AD patients, increased (chapter 4) and decreased (chapter 5) activation was observed.

The increased activation of the vmPFC in elderly during encoding of routes was suggested to be due to inhibition failure (chapter 2). However, given the current developments in research regarding this region, it is more likely to be compensatory. For instance, Dennis and colleagues (2008) found more functional coupling between the hippocampus and mPFC during source memory encoding in elderly. Functional connectivity between the vmPFC and the MTL is thought to support integration of new memories (Tse et al. 2007, Wang and Morris 2010), and enhancement of this crosstalk can be compensatory, especially in the absence of a prior associative network, or schema (van Kesteren et al. 2010).

In AD patients, activation of the vmPFC was increased during autobiographical retrieval (chapter 4) and this activation was negatively correlated with size of the hippocampus, indicating a compensatory process. The same area of the vmPFC showed decreased activation in patients during successful recognition of pictures (chapter 5), indicating an inability to compensate. This finding is supported by the decreased functional connectivity between the left hippocampus and the vmPFC during rest in these patients (chapter 5, but see also Grady 2005).

It therefore seems that the vmPFC can compensate for structural hippocampal change, as was observed in AD. In aging, this compensatory process is probably observed to a lesser extent, because the hippocampus stays relatively intact (Insausti et al. 1998, Raz 2005). In AD, this compensatory process appears only available for remote memories, but not when it comes to recently acquired memories.

The retrosplenial cortex (RSC)

Functional differences in the RSC were only observed in healthy elderly (chapter 2). Elderly displayed increased and decreased activity in the RSC (Brodmann area 30), compared to young during recognition of routes, with the increased activation being more medial than the decreased activation. The increased activation covered the whole right RSC, which is in monkeys more involved in visually guided spatial memory (Vann et al. 2009). In humans, studies also indicate a role for right Brodmann area 30 in navigation (for review, see Maguire 2001), which is in line with the route task of chapter 2. The increased activation in elderly therefore could reflect a compensatory mechanism. The decreased activation observed more lateral seems to originate from adjacent areas (along the visual processing stream). Since there are no reports of patients with selective lesions to be able to dissociate between medial and lateral RSC, the concurrent in- and decrease is very hard to interpret. Future studies may investigate if the increased activation is compensatory and related to the activation decrease in its neighbourhood.

In AD patients, gray matter reduction was observed in the RSC in chapter 5, which is in line with previous studies indicating RSC atrophy and hypometabolism (Klunk et al. 2004, Scahill et al. 2002). In addition, the RSC becomes disconnected from the MTL in AD (just as the vmPFC)(Greicius et al. 2004). No activation differences were observed in AD patients in the RSC, but this is probably due to the nature of the tasks (which were not, for instance, tapping into spatial memory).

In conclusion, the RSC seems to be a region that can exhibit compensatory processing in aging during spatial memory. Since no spatial memory was investigated in AD patients, a similar conclusion cannot be drawn with regard to AD. However, given the structural and metabolic damage of the RSC and co-occurrence of disconnection with the hippocampus in AD, it seems unlikely that this area would display compensatory processing, but this remains to be investigated.

Compensation

The studies reported in this thesis denote signs of compensatory processes in aging and AD (Reuter-Lorenz and Lustig 2005):

Increased activation of the right parahippocampal gyrus in elderly indicated additional spatial processing (chapter 2) and increased activation of the vmPFC in elderly probably supported encoding. In chapter 3, it was observed that elderly adopt an additional strategy. Therefore, compensation in aging seems to reflect a wide spectrum of processes that can aid episodic memory.

In AD patients, compensation was observed as increased activation in the LIFG and vmPFC during autobiographical memory retrieval while hippocampal volume decreased (chapter 4). At first sight this might seem contradictory to the reduced activation observed in AD patients during successful recognition, and the functional disconnection from the hippocampus (chapter 5). There is, however, a plausible explanation:

The hippocampus degenerates and becomes disconnected from the vmPFC in AD (chapter 4 and 5, and e.g. Stoub et al. 2006). Consider again that the vmPFC and hippocampus probably have similar roles in linking and integrating distributed neocortical representations (Wang and Morris 2010). With time, the linking of neocortical representations by the hippocampus is transferred to the vmPFC (Takashima et al. 2006, Takashima et al. 2007, van Kesteren et al. 2010) and crosstalk between the hippocampus and vmPFC supports encoding and consolidation. In that case, dysfunction of the hippocampus and disconnection with the vmPFC should lead to impaired episodic memory encoding and consolidation (not investigated in this thesis). As a consequence, retrieval of recent memories is affected (chapter 5). Also, this would lead to impaired storage of new autobiographical memories. This is corroborated by the anterograde amnesia that accompanies AD (for review, see Carlesimo and Oscar-Berman 1992).

In contrast, retrieval of remote memories is not (yet) affected, since these were acquired before disease onset. In addition, retrieval of consolidated memories is less dependent on crosstalk between the hippocampus and the vmPFC, which is the reason the vmPFC can compensate for degeneration of the hippocampus (chapter 4). As remote memories never seem to become totally independent from the hippocampus, eventually, also autobiographical retrieval becomes impaired in AD (e.g. Gilboa et al. 2005).

All in all, it can be concluded that AD-related hippocampal decline not only affects hippocampal function, but also affects functionality of other structures that it is connected to (Buckner 2004, Buckner et al. 2005).

Future studies should investigate encoding and consolidation, and the role of the vmPFC and hippocampus in these processes, in AD, to determine if the retrieval impairments are caused by decreased encoding or consolidation, or both. Furthermore, additional research in elderly can elucidate if these impairments are disease specific, and if they can be attenuated by training.

Even though all the results reported in this thesis were independent of task performance, one can only speak of attempted compensation, because the elderly and AD patients were not able to reach the same level of task performance as their controls (young and healthy elderly). That does not readily mean that there is no or only limited compensation in aging or AD. Future studies may aim to equalize performance over groups since this facilitates interpretation. Also, one could investigate if there is a correlation between activation and behavioural performance, in order to determine if a certain process is compensatory.

A factor that is also of particular influence on results is homogeneity. Homogeneity between groups (e.g. age, gender, scanner type, comorbidity) was a specific aim, but within a group this is harder to control (with the exception of age, gender or disease severity). Especially in aging or disease, there may be substantial (individual) variation in for example regional functionality or use of strategies and one needs to take these factors into account when explaining results. Next to correlation analyses, testing larger groups and meta-analyses can help identify common compensatory processes.

Conclusions

From the findings in this thesis, several conclusions can be drawn:
Elderly, compared to young, are impaired at spatial and strategic episodic memory tests. Besides signs of impairment (like decreased functionality), elderly also show signs of compensation, like using a different strategy, or enhancing spatial processing.

AD patients, compared to healthy elderly, are impaired at autobiographical, semantic and recognition memory tests. In AD, the hippocampus becomes damaged, and this structural damage underlies functional changes in the hippocampus itself, but also in other areas, like for instance the vmPFC. In this area, compensatory processing was observed. Importantly, this process seems only available for remote memories, since disconnection between the hippocampus and vmPFC prohibits compensation during retrieval of recently acquired memories.
Below, the findings reported in this thesis are displayed in the context of the episodic memory network (**figure 1**)

Outlook

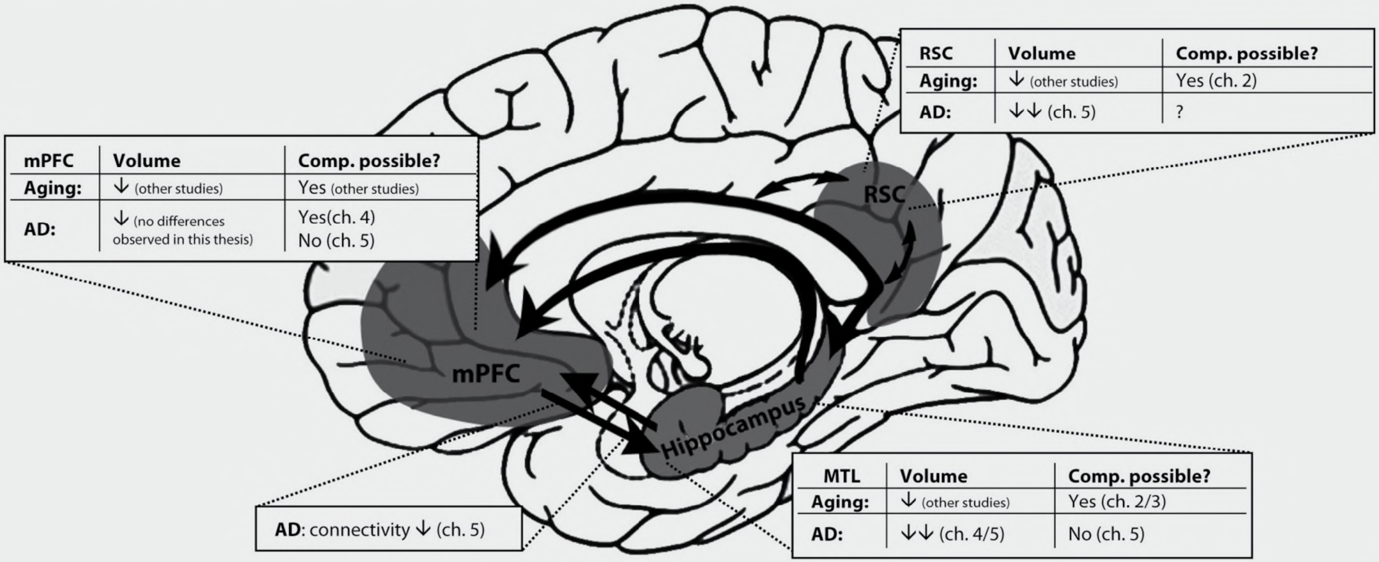
The research discussed in this thesis can be relevant for the diagnostic process in AD and provides insight into how episodic memory in patients and elderly can be trained or optimally utilized.

Neuroimaging in early AD diagnostics

Certainly, there is still a lot to investigate, but one might say that functional changes (like compensatory processing) are occurring already very early in the disease process, even before structural change can be detected. This means that these functional changes can serve as a prognostic, or even diagnostic, tool. As AD is believed to originate decades before clinical onset, a random population of healthy elderly therefore includes future AD patients, which now remain unidentified. Many studies aim at identifying these people, and in the future we might be able to do so, opening the door to early interventions. However, at this moment, the distance to applying fMRI for diagnostic purposes at an individual level in AD is still great. First, the prognostic value of compensatory processes needs to be investigated, before a sensitive test can be developed.

Figure 1

Schematic overview of changes to the episodic memory network in aging and AD. Structural decline is indicated in the tables with arrows. Comp.= compensation; ch.= chapter



Cognitive training

In aging, episodic memory impairment benefits from applying the appropriate strategy or from lowering cognitive demand (for review, see Nyberg 2005). Cognitive demand can be adjusted, as we saw in chapter 3. Companies are already developing products that lower cognitive demand, like navigational devices such as the Tomtom, or easy to use mobile phones and computer software. Probably, aids are also beneficial in AD, which would extend autonomy for these patients and reduce caregiver burden.

Strategic memory can be trained, and helps elderly and patients to cope systematically with cognitively demanding situations and to optimize their performance. Training might aim to reinstate the available range of strategies and teach which strategies are most effective under circumstances. It may also involve unlearning of suboptimal routines, to overcome the perseverance effect that hinders the use of other strategies (Verhaeghen and Marcoen 1996).

As there is large interindividual variability in aging, training should be tailored to individual abilities in order to achieve the largest effect. Lastly, research should aim to determine whether these positive training effects are beneficial to real-world situations.

References

Backman L, Andersson JL, Nyberg L, Winblad B, Nordberg A, Almkvist O. Brain regions associated with episodic retrieval in normal aging and Alzheimer's disease. Neurology 1999; 52: 1861-1870.

Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet 2006; 368: 387-403.

Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991; 82: 239-259.

Buckner RL. Memory and executive function in aging and AD: multiple factors that cause decline and reserve factors that compensate. Neuron 2004; 44: 195-208.

Buckner RL, Snyder AZ, Shannon BJ *et al.* Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory. J Neurosci 2005; 25: 7709-17.

Burgess N, Maguire EA, Spiers HJ, O'Keefe J. A temporoparietal and prefrontal network for retrieving the spatial context of lifelike events. Neuroimage 2001; 14: 439-453.

Byrne P, Becker S, Burgess N. Remembering the past and imagining the future: a neural model of spatial memory and imagery. Psychol Rev 2007; 114: 340-375.

Cabeza R, Daselaar SM, Dolcos F, Prince SE, Budde M, Nyberg L. Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. Cereb Cortex 2004; 14: 364-375.

Carlesimo GA, Oscar-Berman M. Memory deficits in Alzheimer's patients: a comprehensive review. Neuropsychol Rev 1992; 3: 119-169.

Dennis NA, Hayes SM, Prince SE, Madden DJ, Huettel SA, Cabeza R. Effects of aging on the neural correlates of successful item and source memory encoding. J Exp Psychol Learn Mem Cogn 2008; 34: 791-808.

Dickerson BC, Salat DH, Greve DN *et al.* Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. Neurology 2005; 65: 404-411.

Eichenbaum H. A cortical-hippocampal system for declarative memory. Nat Rev Neurosci 2000; 1: 41-50.

Gabrieli JDE. Cognitive neuroscience of human memory. Annual Review of Psychology 1998; 49: 87-115.

Gilboa A, Ramirez J, Kohler S, Westmacott R, Black SE, Moscovitch M. Retrieval of autobiographical memory in Alzheimer's disease: relation to volumes of medial temporal lobe and other structures. Hippocampus 2005; 15: 535-550.

Grady CL. Functional connectivity during memory tasks. In: Cabeza R, Nyberg L, Park D, editors. Cognitive neuroscience of aging; linking cognitive and cerebral aging. New York: Oxford University Press; 2005. p. 286-308.

Grady CL, Maisog JM, Horwitz B *et al.* Age-related changes in cortical blood flow activation during visual processing of faces and location. J Neurosci 1994; 14: 1450-1462.

Greicius MD, Srivastava G, Reiss AL, Menon V. Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. Proc Natl Acad Sci U S A 2004; 101: 4637-4642.

Insausti R, Juottonen K, Soininen H *et al.* MR volumetric analysis of the human entorhinal, perirhinal, and temporopolar cortices. AJNR Am J Neuroradiol 1998; 19: 659-671.

Kessels RP, de Haan EH, Kappelle LJ, Postma A. Varieties of human spatial memory: a meta-analysis on the effects of hippocampal lesions. Brain Res Brain Res Rev 2001; 35: 295-303.

Kim JJ, Fanselow MS. Modality-specific retrograde amnesia of fear. Science 1992; 256: 675-677.

Klunk WE, Engler H, Nordberg A *et al.* Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 2004; 55: 306-319.

Maguire EA. The retrosplenial contribution to human navigation: a review of lesion and neuroimaging findings. Scand J Psychol 2001; 42: 225-238.

Maguire EA, Frith CD. Aging affects the engagement of the hippocampus during autobiographical memory retrieval. Brain 2003; 126: 1511-23.

Moffat SD, Elkins W, Resnick SM. Age differences in the neural systems supporting human allocentric spatial navigation. Neurobiol Aging 2006; 27: 965-972.

Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum RS. The cognitive neuroscience of remote episodic, semantic and spatial memory. Curr Opin Neurobiol 2006; 16: 179-190.

Moscovitch M, Rosenbaum RS, Gilboa A *et al.* Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. J Anat 2005; 207: 35-66.

Nyberg L. Cognitive training in healthy aging. In: Cabeza R, Nyberg L, Park D, editors. Cognitive neuroscience of aging. New York: Oxford University Press; 2005. p. 309-21.

Petrella JR, Wang L, Krishnan S *et al.* Cortical deactivation in mild cognitive impairment: high-field-strength functional MR imaging. Radiology 2007; 245: 224-235.

Raz N. The aging brain observed in vivo: differential changes and their modifiers. In: Cabeza R, Nyberg L, Park D, editors. Cognitive neuroscience of aging; linking cognitive and cerebral aging. New York: Oxford University Press; 2005. p. 19-57.

Reuter-Lorenz PA, Lustig C. Brain aging: reorganizing discoveries about the aging mind. Curr Opin Neurobiol 2005; 15: 245-251.

Scahill RI, Schott JM, Stevens JM, Rossor MN, Fox NC. Mapping the evolution of regional atrophy in Alzheimer's disease: unbiased analysis of fluid-registered serial MRI. Proc Natl Acad Sci U S A 2002; 99: 4703-4707.

Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. J Neuropsychiatry Clin Neurosci 2000; 12: 103-10a.

Sperling RA, Bates JF, Chua EF *et al.* fMRI studies of associative encoding in young and elderly controls and mild Alzheimer's disease. J Neurol Neurosurg Psychiatry 2003; 74: 44-50.

Squire LR, Stark CE, Clark RE. The medial temporal lobe. Annu Rev Neurosci 2004; 27: 279-306.

Stoub TR, Toledo-Morrell L, Stebbins GT, Leurgans S, Bennett DA, Shah RC. Hippocampal disconnection contributes to memory dysfunction in individuals at risk for Alzheimer's disease. Proc Natl Acad Sci U S A 2006; 103: 10041-10045.

Takashima A, Nieuwenhuis IL, Rijpkema M, Petersson KM, Jensen O, Fernandez G. Memory trace stabilization leads to large-scale changes in the retrieval network: a functional MRI study on associative memory. Learn Mem 2007; 14: 472-479.

Takashima A, Petersson KM, Rutters F *et al.* Declarative memory consolidation in humans: a prospective functional magnetic resonance imaging study. Proc Natl Acad Sci U S A 2006; 103: 756-61.

Tse D, Langston RF, Kakeyama M *et al.* Schemas and memory consolidation. Science 2007; 316: 76-82.

Van der Veen FM, Nijhuis FA, Tisserand DJ, Backes WH, Jolles J. Effects of aging on recognition of intentionally and incidentally stored words: an fMRI study. Neuropsychologia 2006; 44: 2477-2486.

van Kesteren MT, Fernandez G, Norris DG, Hermans EJ. Persistent schema-dependent hippocampal-neocortical connectivity during memory encoding and postencoding rest in humans. Proc Natl Acad Sci U S A 2010; 107: 7550-7555.

Vann SD, Aggleton JP, Maguire EA. What does the retrosplenial cortex do? Nat Rev Neurosci 2009; 10: 792-802.

Verhaeghen P, Marcoen A. On the mechanisms of plasticity in young and older adults after instruction in the method of loci: evidence for an amplification model. Psychol Aging 1996; 11: 164-178.

Wang SH, Morris RGM. Hippocampal-Neocortical Interactions in Memory Formation, Consolidation, and Reconsolidation. Annual Review of Psychology 2010; 61: 49-79.

Nederlandse Samenvatting

Functionele veranderingen in het brein gerelateerd aan het episodisch geheugen, bij gezonde veroudering en de ziekte van Alzheimer

Ons dagelijks bestaan is een aaneensluiting van allerlei gebeurtenissen. Vele daarvan leggen we moeiteloos vast: zo hoeven we eigenlijk nooit te zoeken naar onze auto of fiets wanneer we de supermarkt uit lopen. Het opslaan, vasthouden en herinneren van unieke gebeurtenissen met bijbehorende details wordt episodisch geheugen genoemd. De meeste mensen merken dat hun geheugen met toenemende leeftijd wat afneemt: ze hebben meer moeite met het onthouden van namen, het vinden van hun sleutelbos of vergeten producten tijdens het boodschappen doen. Deze lichte afname komt veel voor en past bij neurocognitieve verandering als gevolg van normale veroudering. Echter, veel ouderen hebben juist last van forse geheugenproblemen en ervaren als gevolg hiervan beperkingen in handelen en begrijpen. Wanneer deze beperkingen het dagelijks leven beïnvloeden spreken we van een dementie, meestal veroorzaakt door de ziekte van Alzheimer.

In dit proefschrift heb ik met behulp van functionele beeldvorming van het brein (functional Magnetic Resonance Imaging ofwel fMRI) de hersenactiviteit onderzocht die betrokken is bij het episodische geheugen in het kader van normale veroudering en bij de episodische geheugenstoornissen zoals deze optreden bij de ziekte van Alzheimer.

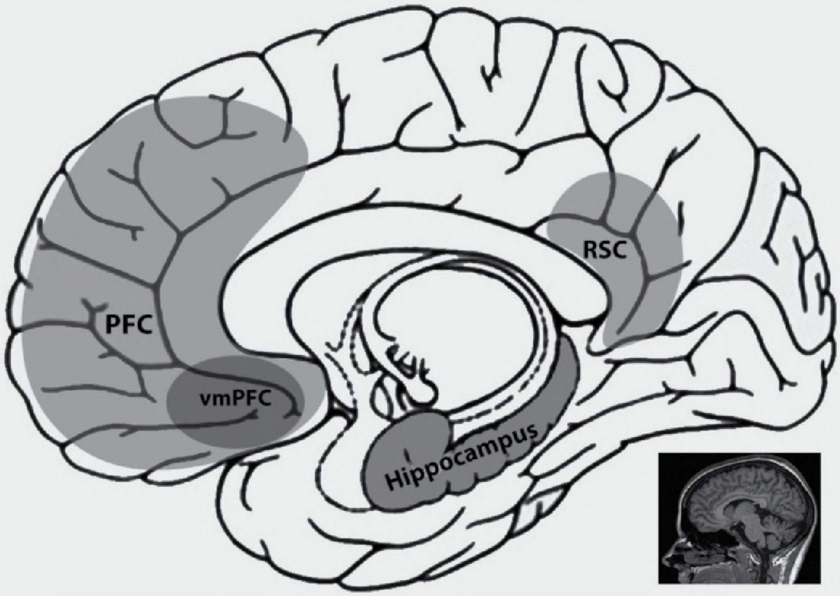
De hersengebieden betrokken bij het episodisch geheugen

Vele hersengebieden ondersteunen het episodisch geheugen, maar er zijn er drie die in het bijzonder hierbij betrokken zijn. Beschadigingen aan deze gebieden zorgen dan ook voor geïsoleerd geheugenverlies: de mediale temporaalkwab (met daarin de hippocampus), de prefrontale cortex (PFC) en de zogenaamde "retrospleniale cortex" (RSC). Deze gebieden zijn weergegeven in figuur 1.

De hippocampus wordt beschouwd als de belangrijkste structuur voor het geheugen: hier komt informatie (tijd, plaats, andere contextuele details) bij elkaar en vindt integratie plaats. Deze structuur zorgt voor het unieke karakter van episodische herinneringen.

De prefrontale cortex is betrokken bij controlerende processen, zoals het gebruik van strategieën om informatie te bewerken. Daarnaast zijn er aanwijzingen dat een

Figuur 1
De hersengebieden betrokken bij het episodisch geheugen; de prefrontale cortex (PFC) met daarin de ventromediale prefrontale cortex (vmPFC), retrospleniale cortex (RSC) en de mediale temporaalkwab met daarin de hippocampus.



onderdeel van dit gebied (de vmPFC) ook een bijdrage levert aan integratie, met name tijdens en na consolidatie van herinneringen.

De functie van de RSC in het geheugen is nog grotendeels onduidelijk, maar vaak wordt activiteit gezien tijdens taken die het ruimtelijk geheugen, navigatie, maar ook autobiografisch geheugen aanspreken. Dit gebied fungeert mogelijk als buffer (tijdelijke opslag).

De ziekte van Alzheimer

De ziekte van Alzheimer is een dementiesyndroom dat genoemd is naar Dr. Aloïs Alzheimer, die de eerste patiënt beschreef. Het is een "neurodegeneratieve" ziekte: zenuwcellen sterven af, in dit geval door een neerslag van eiwitten, beginnend in de mediale temporaalkwab. Daardoor krimpt de hippocampus, wat leidt tot toenemende vergeetachtigheid bij de patiënt. Ook andere klachten, zoals taalproblemen, ontstaan naarmate de ziekte vordert. Als gevolg hiervan neemt de zelfredzaamheid sterk af. Doordat de aandoening voortschrijdt, overlijden patiënten meestal na 8-12 jaar ten gevolge van een secundaire aandoening, zoals longontsteking of hart- en vaatziekten.

Door de hedendaagse vergrijzing zal het aantal Alzheimerpatiënten toenemen naar meer dan 350.000 in 2050. Wereldwijd zal 1 op de 10 ouderen boven de 65 te maken krijgen met de ziekte, wat een nog niet eerder vertoonde uitdaging betekent voor de zorgsystemen van menige natie.

De invloed van veroudering en de ziekte van Alzheimer op de hippocampus, prefrontale cortex en retrospleniale cortex

Zowel gezonde veroudering als de ziekte van Alzheimer beïnvloeden de structuur en functie van de drie bovengenoemde hersengebieden. Gezonde veroudering gaat met name gepaard met een volumeafname van de prefrontale cortex, terwijl bij de ziekte van Alzheimer de afname van het hippocampusvolume op de voorgrond staat. De functionele veranderingen waarmee veroudering en Alzheimer gepaard gaan, zijn representatief voor de onderliggende structurele veranderingen: gezonde ouderen hebben voornamelijk problemen met het strategische aspect van geheugen, terwijl Alzheimerpatiënten een algehele achteruitgang van het geheugen laten zien. De RSC vormt een uitzondering: onderzoeken wijzen erop dat de functionele veranderingen in dit gebied veel groter zijn dan het volumeverlies: de communicatie tussen de RSC en hippocampus neemt af, en in een vroeg stadium van Alzheimer is er al een sterk verlaagd metabolisme in dit gebied te meten, welke zelfs gecorreleerd is aan de neerslag van Alzheimer specifieke eiwitten.

6

Compensatie

Een verandering in structuur of functie van een hersengebied leidt niet altijd of direct tot een verandering op gedragsniveau: de prestatie op bijvoorbeeld een geheugentaak kan gelijk blijven bij aantasting van een betrokken hersengebied. Dat komt doordat er vele compensatoire processen kunnen worden ingezet. Iemand kan een andere strategie gebruiken om een taak op te lossen, maar het is ook mogelijk dat het "onderpresterende" hersengebied harder gaat werken, of een ander hersengebied mee gaat helpen.

Compensatoire processen kunnen klinische symptomen uitstellen en zullen daarom met name vroeg in het ziekteproces voorkomen. Dit maakt ze zeer geschikt als mogelijke biomarker voor vroegdiagnostiek, zodat er in de toekomst wellicht eerder ingegrepen kan worden. Zowel compensatoire processen, als structurele en functionele veranderingen in het brein, kunnen zeer goed gemeten worden met (functionele) MRI.

(Functionele) MRI

De onderzoeken in dit proefschrift zijn allemaal uitgevoerd met behulp van een MRI-scanner (MRI = Magnetic Resonance Imaging). Door gebruik te maken van een sterk constant magneetveld en radiogolven, kan de MRI-scanner ("structurele") beelden maken van de hersenen.

Ook de hersenactiviteit kan gemeten worden: dit wordt functionele MRI (fMRI) genoemd. De scanner kan namelijk veranderingen in de zuurstofvoorziening van hersengebieden meten en omdat de activiteit van zenuwcellen gecorreleerd is aan de zuurstofvoorziening via het bloed, zijn deze veranderingen in zuurstofvoorziening een afspiegeling van hersenactiviteit. Hersenactiviteit kan met fMRI tot op de millimeter en enkele seconden nauwkeurig gemeten worden.

Figuur 2
De MRI-scanner van het Donders Centre for Cognitive Neuroimaging.

De onderzoeken in dit proefschrift: gezonde veroudering

In hoofdstuk 2 en 3 heb ik het effect van gezonde veroudering op het ruimtelijk geheugen onderzocht, en de strategische processen die daarbij betrokken zijn.

Het eerste onderzoek omvatte het opslaan en herkennen van routes door virtuele huizen: hieruit bleek dat ouderen veel moeite hadden de routes te herkennen. In de hersenen werd er verlaagde activiteit waargenomen in (onder andere) de vmPFC, wat duidde op een verminderde opslag van de informatie door de ouderen. Tijdens route-herkenning werd er een verhoogde activiteit waargenomen in de mediale temporaal-kwab en de RSC, wat waarschijnlijk compensatoire processen zijn.

Tijdens het tweede onderzoek leerden deelnemers de plaatsen van negen objecten in een raamwerk te onthouden. Vervolgens probeerden ze de objecten tijdens de herinneringsfase weer terug op de juiste plek te leggen. In de aanleerfase werd de hoeveelheid ruimtelijke informatie gemanipuleerd: óf de deelnemers zagen alle objecten tegelijk in het raamwerk, óf ze zagen de objecten 1 voor 1 (lijkend op het spel memory). Zie ook figuur 3.1. Door middel van deze manipulatie kon onderzocht worden of veroudering effect heeft op het gebruik van extra ruimtelijke informatie. De jongeren maakten systematisch gebruik van de extra informatie: zij vulden het raamwerk door de objecten naast elkaar te plaatsen. De ouderen deden dit niet en tijdens fMRI lieten zij een verhoogde activiteit zien in de mediale temporaal kwab en in een zogenaamd "frontaal-striataal" netwerk, wat erop duidde dat ouderen én het episodisch geheugen meer aanspraken én andere strategieën verkenden. Ook dit kan gezien worden als compensatie.

De onderzoeken in dit proefschrift: de ziekte van Alzheimer

In hoofdstuk 4 heb ik het effect van de ziekte van Alzheimer op het autobiografisch geheugen onderzocht bij gezonde ouderen en Alzheimerpatiënten. Autobiografische interviews met de deelnemers lieten zien dat Alzheimerpatiënten hun autobiografische herinneringen "semantiseren", wat betekent dat deze persoonlijke herinneringen niet zozeer meer gebaseerd zijn op het episodisch geheugen, maar meer op het geheugen voor feiten. Het lijkt er dus op dat patiënten autobiografische herinneringen niet zo gedetailleerd herbeleven als gezonde ouderen. In de hersenen werd bij de patiënten een verhoogde activiteit gezien in (onder andere) de vmPFC (zie ook het kopje "De hersengebieden betrokken bij het episodisch geheugen"). Opvallend was dat de activiteit in dit gebied bij patiënten hoger was naarmate de hippocampus kleiner was. Dit duidde erop dat de activiteit in de vmPFC als compensatie werkt tegen het volumeverlies van de hippocampus.

Daarom zijn in hoofdstuk 5 de structuur en functie van de vmPFC en hippocampus nader onderzocht met meerdere meettechnieken: (1) de prestatie op een foto-herkenningstaak; (2) de structuur van de hersenen; (3) de hersenactiviteit tijdens succesvolle herkenning van foto's en (4) functionele connectiviteit (oftewel communicatie) tussen de vmPFC en hippocampus. Uit de resultaten bleek dat Alzheimerpatiënten meer moeite hadden de foto's te herkennen. De structurele achteruitgang was beperkt tot de mediale temporaalkwab (met hippocampus); de vmPFC was dus niet aangedaan. De hersenactiviteit in zowel de vmPFC als de hippocampus van de patiënten was verminderd tijdens de herkenning van foto's, net als de communicatie tussen deze twee gebieden.

Het lijkt er dus op dat de functionele achteruitgang van de vmPFC bij Alzheimer-patiënten te wijten is aan de structurele en functionele achteruitgang van de hippocampus, waarschijnlijk doordat de verbinding tussen de gebieden verbroken raakt. De vmPFC kon de hippocampus dus niet ondersteunen tijdens de foto herkenningstaak.

Deze conclusie lijkt tegenstrijdig met het onderzoek naar autobiografisch geheugen, waar de vmPFC de hippocampus wél kon ondersteunen. Toch hoeft dat niet zo te zijn. In het autobiografisch onderzoek zijn de herinneringen namelijk oud, en waarschijnlijk al opgeslagen voordat de ziekte zijn intrede deed. Bij de fotoherkenningstaak zijn de herinneringen nog heel "vers" (maximaal 1 uur oud). Compensatie door de vmPFC is dus blijkbaar alleen mogelijk voor oude herinneringen; dit komt overeen met de observatie dat Alzheimerpatiënten moeite hebben met het vormen van nieuwe autobiografische herinneringen. Daarnaast blijkt dat de structurele achteruitgang van de hippocampus bij patiënten met de ziekte van Alzheimer niet alleen een negatief effect heeft op zijn eigen functie, maar ook op de functie van gebieden waarmee het in verbinding staat.

Conclusies

Dit proefschrift heeft tot verschillende inzichten geleid:
Ondanks de verminderde prestatie op episodisch geheugentaken, laten gezonde ouderen ook veel compensatie zien, zoals het gebruik van een andere strategie, of het inzetten van meer activiteit in betrokken hersengebieden.

Ook Alzheimerpatiënten hebben een verminderde prestatie op episodisch geheugen-taken. Daarnaast leidt de schade aan de hippocampus niet alleen tot verminderde functie van de hippocampus zelf, maar ook tot functievermindering van hersengebieden waarmee het verbonden is, zoals de vmPFC. Het compensatoire proces in de vmPFC is door die schade alleen beschikbaar voor oude herinneringen, omdat de verminderde communicatie tussen de vmPFC en hippocampus voorkomt dat het beschikbaar is voor nieuwe herinneringen.

Betekenis van de uitkomsten

De ziekte van Alzheimer gaat gepaard met functionele veranderingen die waarschijnlijk al zeer vroeg in het ziekteproces detecteerbaar zijn. En hoe vroeger de ziekte gedetecteerd kan worden, des te vroeger de mogelijkheid tot ingrijpen. De compensatoire processen beschreven in dit proefschrift zijn dus niet alleen basis voor vroege diagnostiek, ze zijn ook nuttig voor interventie: ze tonen aan hoe weerbaar het brein is, en bovendien zijn veel van deze processen trainbaar. Zo is het bijvoorbeeld mogelijk mensen te leren welke strategie het meest efficiënt is in bepaalde situaties. Ook loont het de moeite te realiseren dat het brein constant aan verandering onderhevig is. Wat voor jongeren logisch of makkelijk is, is dat misschien niet voor ouderen, laat staan Alzheimerpatiënten. Hulpmiddelen die de belasting op het denkvermogen verlagen, zoals de TomTom of speciale mobiele telefoons, kunnen de autonomie van ouderen en patiënten dus aanzienlijk vergroten.

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Publications

Meulenbroek, O, Petersson, KM, Voermans, N, Weber, B, Fernández, G (2004)**.** Age differences in neural correlates of route encoding and route recognition. *Neuroimage* 22(4):1503-14.

Meulenbroek, O, Kessels, RPC, de Rover, M, Petersson, KM, Olde Rikkert, MGM, Rijpkema, M, Fernández, G (2010). Age-effects on associative object-location memory. *Brain Research.* 1315:100-10.

Meulenbroek, O, Rijpkema, M, Kessels, RPC, Olde Rikkert, MGM, Fernández, G (2010). Autobiographical memory retrieval in patients with Alzheimer's disease. *Neuroimage* 53(1):331-40.

Meulenbroek, O, Vernooij-Dassen, M, Kessels, RPC, Graff, MJL, Sjögren, MJC, Schalk, BWM, Hoogsteen-Ossewaarde, ME, Claassen, JAHR, Melis, RJF & Olde Rikkert, MGM (2010). Informed consent in dementia research. Legislation, theoretical concepts and how to assess capacity to consent. *European Geriatric Medicine* 1 (1): 58-63.

Kessels, RPC, **Meulenbroek, O**, Fernandez, G, Olde Rikkert, MGM (2010). Spatial Working Memory in Aging and Mild Cognitive Impairment: Effects of Task Load and Contextual Cueing. *Neuropsychology, development and cognition. Section B, Aging, neuropsychology and cognition*, in press.

Meulenbroek, O, Rijpkema, M, Kessels, RPC, Olde Rikkert, MGM, Fernández, G. Hippocampal decline in Alzheimer's disease affects ventromedial prefrontal cortex functioning. Submitted for publication.

Curriculum Vitae

Olga Meulenbroek was born in Nieuwegein on April 19th 1981. She graduated from high school at "De Nieuwe Veste" in Coevorden in 1999. In 2004, she acquired her MSc degree in Biology with honor at the Radboud University Nijmegen. After working a short period as a research assistant, she started in 2005 as PhD student at the Donders Institute for Brain, Cognition and Behaviour and the Department of Neurology at the Radboud University Nijmegen Medical Centre. The work during that period resulted in this thesis.

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Olga Meulenbroek is geboren in Nieuwegein op 19 april 1981. Ze slaagde in 1999 voor het gymnasium aan "De Nieuwe Veste" te Coevorden. In 2004 studeerde ze 'met genoegen' af aan de studie biologie aan de Radboud Universiteit Nijmegen. Na een korte periode als onderzoeksassistent begon zij in 2005 als junioronderzoeker bij het Donders Institute for Brain, Cognition and Behaviour en de afdeling Neurologie van het UMC St. Radboud. De resultaten van het onderzoek in die periode resulteerde in dit proefschrift.

Olga Meulenbroek werkt op dit moment bij de afdeling Geriatrie van het UMC St Radboud, waar ze, onder andere, coördinator is van het Alzheimer Centrum Nijmegen.

Series Donders Institute for Brain, Cognition and Behaviour

1. van Aalderen-Smeets, S.I. (2007). *Neural dynamics of visual selection.* Maastricht University, Maastricht, The Netherlands.
2. Schoffelen, J.M. (2007). *Neuronal communication through coherence in the human motor system.* Radboud University Nijmegen, Nijmegen, The Netherlands.
3. de Lange, F.P. (2008). *Neural mechanisms of motor imagery.* Radboud University Nijmegen, Nijmegen, The Netherlands.
4. Grol, M.J. (2008). *Parieto-frontal circuitry in visuomotor control.* University Utrecht, Utrecht, The Netherlands.
5. Bauer, M. (2008). *Functional roles of rhythmic neuronal activity in the human visual and somatosensory system.* Radboud University Nijmegen, Nijmegen, The Netherlands.
6. Mazaheri, A. (2008). *The Influence of Ongoing Oscillatory Brain Activity on Evoked Responses and Behaviour.* Radboud University Nijmegen, Nijmegen, The Netherlands.
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